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CONTENTS

Thyroid-Adrenocortical Interrelations Following Operation. *Ira S. Goldenberg, M.D., Leo Lutwak, Ph.D., Paul J. Rosenbaum, M.S., and Mark A. Hayes, M.D., Ph.D., F.A.C.S., New Haven, Connecticut* 513

Physiologic and Metabolic Changes During Autogenous Lobe Oxygenation with Total Cardiac By-Pass Employing the Azygos Flow Principle. *Morley Cohen, M.D., Herbert E. Warden, M.D., and C. Walton Lillehei, M.D., F.A.C.S., Minneapolis, Minnesota* 523

Primary Carcinoma of the Gallbladder. *Brooke Roberts, M.D., F.A.C.S., Philadelphia, Pennsylvania* 530

Infection in Burns—I, The Problem and Evaluation of Therapy. *N. Carl-Fredrik Liedberg, Ludwig R. Kuhn, Ph.D., Lt. Col., M.S.C., Benjamin A. Barnes, M.D., Capt., M.C., Eric Reiss, M.D., Capt., M.C., and William H. Amspacher, M.D., Col., M.C., U.S.A., Fort Sam Houston, Texas* 535

Some Hormonal Aspects of Human Parturition with Particular Reference to the Neurohypophysis. *Robert C. Hickey, M.D., F.A.C.S., and William C. Keettel, M.D., F.A.C.S., Iowa City, Iowa* 541

Postoperative Pseudomembranous Enterocolitis. *Jacqueline D. Pettet, M.D., Archie H. Baggenstoss, M.D., William H. Dearing, M.D., and Edward S. Judd, Jr., M.D., F.A.C.S., Rochester, Minnesota* 546

Treatment of Patellar Fractures; Review of 68 Consecutive Surgical Cases. *Rudolph S. Reich, M.D., F.A.C.S., and Norman J. Rosenberg, M.D., F.A.C.S., Cleveland, Ohio* 553

Surgical Management of Mandible Invaded by Oral Cancer. *Louis T. Byars, M.D., F.A.C.S., St. Louis, Missouri* 564

Papillary Cystadenoma Lymphomatosum. *M. C. Wheelock, M.D., and C. M. Strand, M.D., Chicago, Illinois* 571

Urinary and Fecal Incontinence Due to Congenital Abnormalities in Children; Management by Implantation of the Ureters into an Isolated Ileostomy. *Alexander H. Bill, Jr., M.D., F.A.C.S., David H. Dillard, M.D., Harold E. Eggers, M.D., and Ole Jensen, Jr., M.D., Seattle, Washington* 575

Invasive Adenoma of the Thyroid; Analysis of 46 Cases. *V. E. Chesky, M.D., F.A.C.S., W. C. Dreese, M.D., and C. A. Hellwig, M.D., Halstead, Kansas* ... 581

Aseptic Necrosis of the Femoral Head in Dogs; Effect of Drilling and Bone Grafting. *Michael Bonfiglio, M.D., F.A.C.S., Iowa City, Iowa* 591

The Effect of Positive and Negative Pressure Respiration on Unilateral Pulmonary Blood Flow in the Open Chest. *Jay L. Ankeney, M.D., Charles A. Hubay, M.D., F.A.C.S., Paul R. Hackett, M.D., and Robert A. Hingson, M.D., F.A.C.A., F.I.C.A., Cleveland, Ohio* 600

CONTENTS CONTINUED ON PAGE 7

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CONTENTS FOR MAY 1954—CONTINUED

In Support of Surgical Removal of Small Ulcerating Lesions of the Stomach Without Benefit of Medical Treatment. *J. E. Strode, M.D., F.A.C.S., Honolulu, Hawaii* 607

The Replacement of Segments of the Thoracic Esophagus by Polythene Tubes. *H. D. Moore, M.C., M.B., B.S.(Sydney), F.R.C.S.(Edin.), F.R.C.S.(Eng.), Leeds, England* 619

Placenta Previa and Previous Lower Segment Cesarean Section. *S. Bender, M.D., F.R.C.S.E., M.R.C.O.G., Liverpool, England* 625

EDITORIALS

Diagnostic Laparotomy in Chronic Abdominal Disease. *P. H. T. Thorlakson, M.D., F.A.C.S., Winnipeg, Canada* 629

Caustic Burns of the Esophagus. *Leon J. Leahy, M.D., Buffalo, New York* 631

THE SURGEON AT WORK

A New Instrument to Facilitate Transduodenal Sphincterotomy. *Henry Doubilet, M.D., F.A.C.S., New York, New York* 634

THE SURGEON'S LIBRARY

REVIEWS OF NEW BOOKS

Human Embryology. By Bradley M. Patten. 2nd ed. 636

A Source-Book of Medical Terms. By Edmund C. Jaeger 636

The Fundamentals of Radiography. Medical Division, Eastman Kodak Company. 8th ed. 636

Allgemeine und spezielle chirurgische Operationslehre. By Martin Kirschner. 2nd ed. Edited by N. Guleke and R. Zenker. Vol. VII, part 1—Die Eingriffe in der Bauchhoehle. New revision by Dr. Rudolf Zenker 636

Clinical Obstetrics. By Members of the Staff of the Pennsylvania Hospital. Edited by Clifford B. Lull and Robert A. Kimbrough 637

Fundamentals of Clinical Cancer; with Emphasis on Early Diagnosis and Treatment. By Leonard B. Goldman 637

Gastrectomia parcial; resultados na úlcera gástrica e duodenal. By Lúcio Galvão 638

Physical Examination of the Surgical Patient. By J. Englebert Dunphy and Thomas W. Botsford 638

Essential Urology. By Fletcher H. Colby. 2nd ed. 638

A Handbook of Radiotherapy. By Walter M. Levitt 639

Inhalation Therapy and Resuscitation. By Meyer Saklad 639

Operative Surgery. By Guy W. Horseley and Isaac A. Bigger. Vols. I and II. 6th ed. 639

Books Received 640

INTERNATIONAL ABSTRACTS OF SURGERY

Contents ..... i-viii

Collective Reviews: Current Status of Antimicrobial Therapy in Genitourinary Tuberculosis. *James W. Faulkner, M.D., David T. Carr, M.D., and John L. Emmett, M.D., Rochester, Minnesota* 417–426

Stress Incontinence in the Female. *John C. Ullery, M.D., F.A.C.S., Philadelphia, Pennsylvania* 427–433

Abstracts of Current Surgical Literature 434–520

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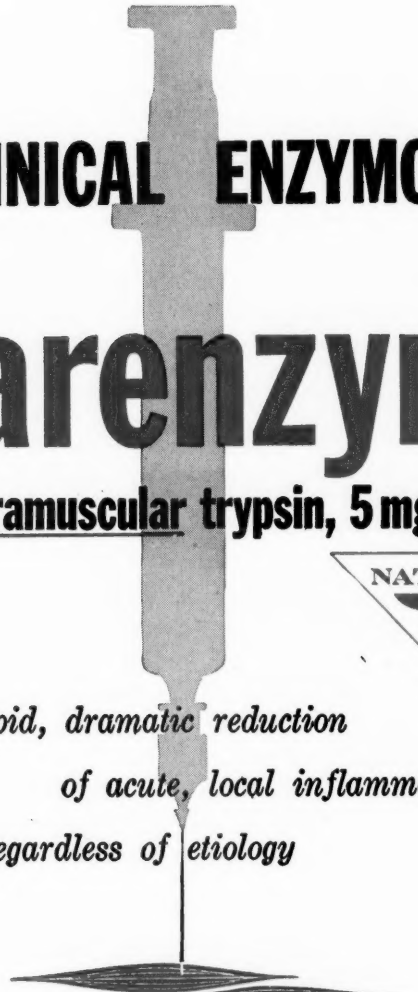

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SURGERY
GYNECOLOGY AND OBSTETRICS

VOLUME 98 MAY, 1954 NUMBER 5

THYROID-ADRENOCORTICAL INTERRELATIONS FOLLOWING OPERATION

IRA S. GOLDENBERG, M.D., LEO LUTWAK, Ph.D., PAUL J. ROSENBAUM, M.S., and MARK A. HAYES, M.D., Ph.D., F.A.C.S., New Haven, Connecticut

MANY alterations in normal metabolism which follow stress in the human organism have been clarified to some extent by the recognition of the existence of a responding pituitary-adrenocortical axis. Endogenous release following trauma or exogenous administration of adrenocorticotrophic hormone appears to cause identical metabolic responses. An increase in adrenocortical activity alone, however, is not responsible for the inconstant responses observed after operation since it has been demonstrated by Ingle and associates that adrenalectomized animals maintained on constant amounts of adrenocortical hormones will display an increase in nitrogen excretion if subjected to trauma. It has been demonstrated further in animals by Koelsche and Kendall that adrenocortical hormones are antagonistic to the excessive nitrogen excretion which accompanies thyroxin-induced hypermetabolism and Gribble and Peters showed that the nitrogen loss following thermal burns is abolished if preceded by thyroidectomy.

These experimental findings in animals make it necessary, therefore, to search elsewhere for additional factors which mediate the response of man to trauma. Numerous investigations of thyroid-adrenocortical interrelations have been made in man and animals under experimentally induced hyperadrenocortical and posttraumatic conditions; in these, thyroid function has been reported to be decreased, increased, or to undergo no constant change. If a full understanding of the response of the organism to trauma is to be made available, it is important that the role of each functioning component of the neuroendocrine system be evaluated. The present investigation was planned to study the role that the thyroid gland plays in the multiple readjustments within the human subject following trauma in a rigidly controlled environment and the relationship of thyroid activity during the posttraumatic period to that of the adrenocortex.

From the Samuel C. Harvey Metabolic Unit, Department of Surgery, Yale University School of Medicine, New Haven, Connecticut.

This study was made possible by funds obtained from the Medical Fluid Research Funds of Yale University; from a gift by the Order of the Eastern Star to the Department of Surgery, Yale University, and from an Institutional Grant by the American Cancer Society to Yale University.

MATERIALS AND METHODS

This investigation included the following patient-subjects: a hypothyroid female, 2 euthyroid females, a slightly hyperthyroid male, and a slightly hyperthyroid female who had received propylthiouracil for 3 weeks prior to operation. All patients were presumed initially to have normal adrenocortical function.

The patients received a daily diet prorated on calculated body surface and standardized to include 1,600 calories, 10 grams of nitrogen,

2 grams of sodium, and 2,000 milliliters of tap water per 1.73 square meters of body surface. The total daily intake was measured carefully and to verify the diet calculations, a homogenized mixture of all food and water consumed during any 24 hour period by each subject was analyzed for nitrogen, sodium, and potassium content. All of the subjects were co-operative and consumed all of the calculated diet each day. Equivalent deductions were made from the day's oral intake of water and calories in those patients who received parenteral fluids during the study period.

A refrigerator at the bedside of the patient was used for storage of 24 hour urine specimens, thus eliminating the need for preservatives. The collections were started and completed at 8:00 a.m. daily, and all food and fluid were ingested prior to midnight so that each collection truly represented a 24 hour period. Urine was not collected on the day of operation to eliminate alterations in intake necessarily present on this day because of possible parenteral fluid and blood administration.

Each 24 hour urine specimen was analyzed for nitrogen, total inorganic phosphorus, sodium, potassium, uric acid, creatinine, and creatine. Total inorganic phosphorus excretion was determined in order to check the values of nitrogen excretion since they tend to parallel each other. Nucleoprotein metabolism was reflected in the uric acid excretion and the latter when related to the creatinine excretion was an indicator of adrenocortical activity as shown by Forsham and associates. Creatinine excretion which remains essentially constant in the absence of kidney disease indicated the completeness of the urinary collections. In the present study adequacy of renal function was determined by creatinine clearance and normal values were found in all subjects. Means believes that thyroid activity from day to day is reflected in the creatine excretion and this determination, therefore, was very important in the present study.

Urinary excretory end-products of adrenocortical steroids including 17-ketosteroids, corticosteroids, and Pettenkofer chromogens were determined. The 17-ketosteroids and the Pettenkofer chromogens are expressed as milligrams of dehydroisoandrosterone while the corticosteroids are expressed as milligrams of desoxycorticosterone. Pettenkofer chromogens (dehydroepiandrosterone) analysis was included here because Wolfson believes that corticosterone is the major precursor of this material.

Fecal specimens, collected in some of the patients for 3 and 4 day periods, were frozen at —20 degrees F. during the collection period and homogenized aliquots of the specimens were then analyzed for nitrogen, sodium, and potassium content to determine the constancy of these constituents. Ingestion of a carmine red capsule served as an indicator of the start and end of each sample by staining the feces appropriately.

Radioactive iodine thyroid uptake and urinary excretion were employed as measures of thyroid activity. Oral and intravenous routes of administration were used but only one method in any single subject. Material for oral ingestion was freshly prepared from a stock solution of I^{131} and was administered in 60 milliliters of tap water without carrier being present. The glass containing the I^{131} was rinsed 5 times and this rinse water was also given to the patient to assure that the full amount of I^{131} had been given. Benzyl alcohol (0.9 per cent) was added to the intravenously administered radioiodine as a bacteriostat. A highly efficient, bismuth-coated cathode counting tube shielded with 3 millimeters of lead and with an effective length of 15 centimeters was used for determination of the radioactivity, in which the maximum allowable error is considered to be 3 per cent. Thyroid gland concentration of the I^{131} was estimated by positioning the tube 25 centimeters from the anterior neck (with constant, fixed reference points) so that all functioning thyroid tissue in the neck region was exposed to the tube. Counts of radioactivity taken over the thigh were subtracted from the neck counts as representing background activity and extrathyroidal radioiodine. The I^{131} uptake is expressed as a percentage of the total amount given and was determined by comparing the neck count (minus background activity) with a solution containing the same amount of I^{131} administered. This latter solution was exposed to the counting tube at a distance of

25 centimeters in a 50 milliliter capacity glass bottle to simulate as closely as possible the thyroid glandular area and volume. Measurements of thyroid concentration of the radioiodine were made at 1, 3, 6, and 24 hours after the material had been administered (except patient E.M. in whom only a 6 hour count was made) and every 24 hours thereafter for 3 days.

The urinary excretion of the I^{131} was measured by exposure of a standard glass vessel containing all of the urine for a given period of time to the bismuth counting tube 25 centimeters distant. An amount of radioiodine equivalent to the administered dose was placed in an identical glass container, was diluted to the same volume as the urine sample with distilled water and was then counted as a standard in the same manner. The excretion is expressed as a percentage of the total amount of I^{131} administered. Urinary excretion was determined for 12 hour periods for the first 24 hours after administration in all patients (except E.M.) and then in successive 24 hour samples until no activity could be detected.

All measurements of radioactivity were conducted for 4 minute periods providing a statistically significant number of counts. For the cases in which administrations of I^{131} were repeated within short periods of time, the newer standard solution always included the previous amount administered (taken from the original dilution) thus correcting for residual radioactivity in the gland.

Butanol-extractable iodine (BEI) determinations in postabsorptive serum were also done according to the method of Man and associates in all patients as another indicator of the level of thyroid activity. The values for serum iodine determined in this manner compare closely with those for serum protein-bound iodine. It should be noted that in all cases the immediate postoperative specimen for this analysis was drawn from 18 to 24 hours following completion of the operative procedure.

Operation in all cases was under general anesthesia with endotracheal intubation thus insuring maximal stimulation to the patient where the procedure itself might be considered to be minimally traumatic.

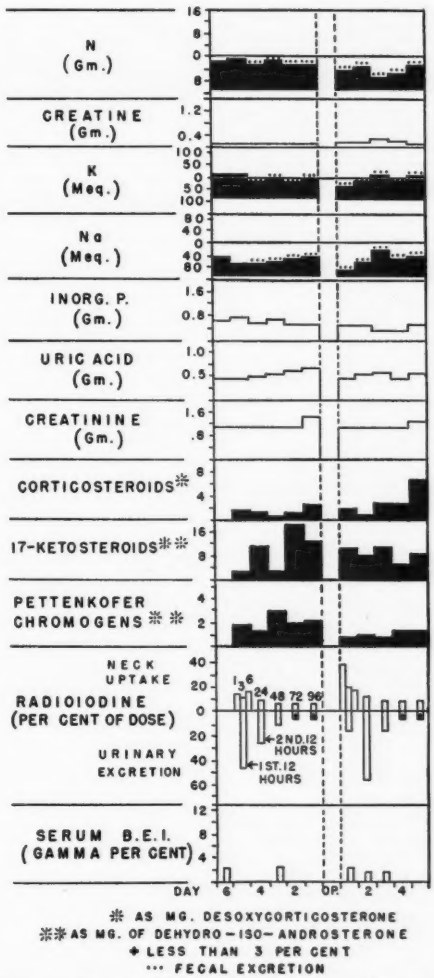

Fig. 1. Patient E.McC. Metabolic data have been charted according to the method of Reifenstein, Albright, and Wells. Numbers over bars in radioiodine chart refer to hours after administration of I^{131} that counts were taken.

RESULTS

CASE 1. E.McC. (Fig. 1), a 54 year old female, had undergone a total thyroidectomy and a left radical neck dissection 1 year previously for a nonfunctioning thyroid cancer. A mass in the scar of the neck dissection prompted hospital admission and prior to entry for excision maintenance thyroid medication (0.2 gram daily) had been discontinued for 3 weeks to insure the existence of a hypometabolic state at the time of operation.

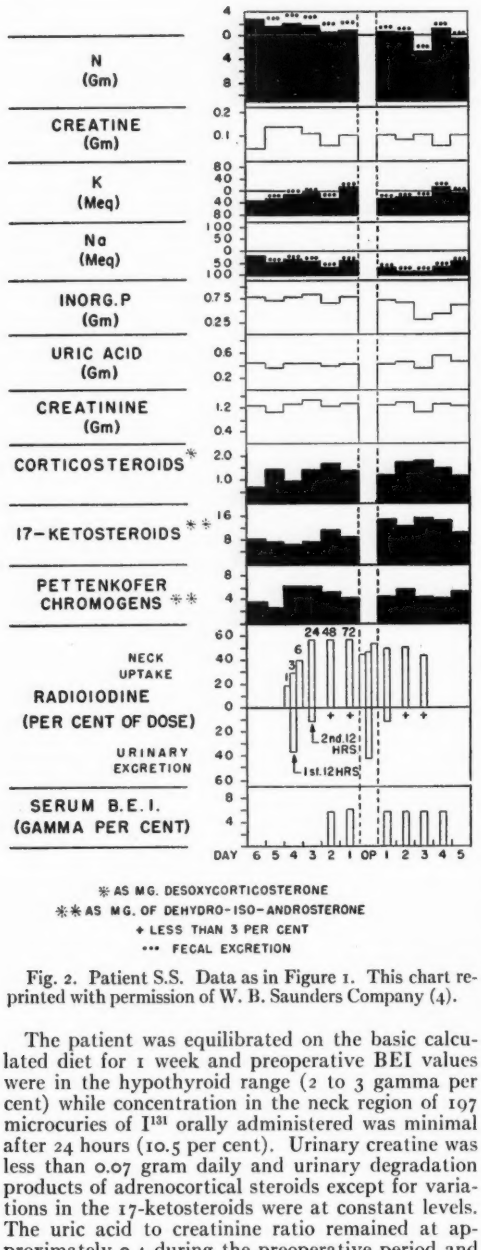

Fig. 2. Patient S.S. Data as in Figure 1. This chart reprinted with permission of W. B. Saunders Company (4).

The patient was equilibrated on the basic calculated diet for 1 week and preoperative BEI values were in the hypothyroid range (2 to 3 gamma per cent) while concentration in the neck region of 197 microcuries of I^{131} orally administered was minimal after 24 hours (10.5 per cent). Urinary creatine was less than 0.07 gram daily and urinary degradation products of adrenocortical steroids except for variations in the 17-ketosteroids were at constant levels. The uric acid to creatinine ratio remained at approximately 0.4 during the preoperative period and during the same period a slightly positive nitrogen balance existed.

Before operation it was not possible to determine accurately whether the radioactivity in the neck represented concentration of the I^{131} in remnants of normal thyroid gland or in functioning tumor. The radically excised specimen, however, revealed only granulation tissue and foreign body reaction so that it became clear after operation that the radioactivity in the neck represented concentration by residual normal gland.

Twenty-four hours after operation 171 microcuries of radioiodine were given orally and a definitely increased concentration in the neck was noted at 1, 3, and 6 hours after administration when compared to the preoperative uptake study. The increased concentration was approximately four times the preoperative level at 1 hour, and the first 12 hour urinary excretion was less than one-half the preoperative excretion for the same period of time. These findings indicated a definitely increased thyroid activity after the surgical procedure. Radioactivity in the neck 24 hours after administration of the I^{131} (48 hours after operation) closely paralleled the preoperative measurement as did also the 24 hour urinary excretion. The serum BEI level did not change appreciably, remaining at approximately 2 gamma per cent through the days immediately following operation.

The postoperative urinary creatine excretion more than doubled that obtained preoperatively corroborating the radioiodine measurements of increased thyroid activity after operation. Significant adrenocortical stimulation was noted since the urinary corticosteroids increased from the levels before operation but the uric acid to creatinine ratio remained approximately 0.4. A small but definite decrease in urinary nitrogen was evident after operation and a brief, moderate sodium retention was evident. Positive nitrogen balance persisted throughout the postoperative period of observation though it was evident that there was a significant increase in corticosteroid excretion. With evidence of increased thyroid activity, shown by an increase in creatinuria, and evidence of increased adrenocortical activity, shown by an increase in corticosteroid excretion, there is a definite increase in nitrogen retention, a finding not to be predicted from activation of either system independently.

Fecal excretion of nitrogen, sodium, and potassium remained unchanged from one phase of the study to the next and apparently was unaffected by the various readjustments occurring in this patient.

CASE 2. S.S. (Fig. 2), a 55 year old male, was admitted to the hospital for investigation of a mass in the left breast associated with axillary lymphadenopathy. Equilibration of the patient on the basic diet was carried out for 7 days prior to excision of the lesions. The serum BEI levels during this period (5 to 6 gamma per cent) were in the range of normal values although the uptake in the neck of 55 microcuries of radioiodine administered orally indicated a low hyperthyroid concentration (56 per cent at 24 hours). A slightly negative nitrogen balance was present and no significant abnormalities were noted

otherwise in the urinary analyses. Adrenocortical steroid metabolites in the urine were at fairly constant levels of excretion. The uric acid-creatinine ratio remained stable prior to operation.

Pathologic examination of a frozen section which revealed gynecomastia and hyperplastic lymphadenopathy was followed by complete excision of the lesions. Five hours after operation 43 microcuries of I^{131} were given orally, and considerable increase in the concentration of the material in the thyroid region was noted in comparison to preoperative levels at 1, 3, and 6 hours after administration (preoperative: 1 hour, 19 per cent; 3 hours, 29 per cent; 6 hours, 39 per cent; postoperative: 1 hour, 46 per cent; 3 hours, 47 per cent; 6 hours, 54 per cent). The first 12 hour urinary excretion and the 24 hour concentration in the neck, however, were not increased following operation. Serum BEI determinations were unchanged after operation as was also the urinary excretion of creatine (0.1 gram daily).

Urinary nitrogen remained essentially unchanged after operation while there was a significant increase in the urinary excretion of 17-ketosteroids and corticosteroids; the Pettenkofer chromogens remained at the preoperative levels. The uric acid to creatinine ratio increased slightly and marked sodium retention was evident. Postoperative fecal excretion of nitrogen was one-third that of the preoperative period while sodium and potassium content of the feces did not change. As in the previous patient, this individual responded to operative trauma with metabolism being carried at new higher levels of thyroid and adrenocortical activity. There was, nevertheless, an actual reduction in urinary excretion of nitrogen.

CASE 3. D.M. (Fig. 3), a 28 year old female patient, was admitted for operative treatment because of suspected extensive chronic pelvic inflammatory disease. The basic calculated diet was administered for 1 week prior to operation. Forty-eight microcuries of I^{131} given intravenously (with benzyl alcohol 0.9 per cent as a bacteriostat) was concentrated normally by the thyroid gland (28 per cent after 24 hours), while serum BEI levels averaged 5 gamma per cent. Creatine excretion and urinary sodium and potassium were stable. Adrenocortical metabolites were constant and the uric acid to creatinine ratio varied from 0.2 to 0.3. Preoperative 17-ketosteroid excretions were not determined. A slight positive nitrogen balance was present.

Extensive endometriosis was found at operation and a total hysterectomy with bilateral salpingectomy was performed. No oral intake was permitted during the first 4 days after operation and parenteral fluids daily included 2,500 milliliters of 5 per cent glucose in water and 500 milliliters of normal saline solution with 40 milliequivalents of potassium chloride added. Increased concentration of 40 microcuries of I^{131} given intravenously 24 hours after operation was noted during the early hours (preoperative: 1 hour, 5 per cent; 3 hours, 9 per cent; postoperative: 1 hour, 10 per cent; 3 hours, 11 per cent) after administration, but the 24 hour concentration was markedly depressed when compared to the preoperative test (preoperative, 28 per cent; postoperative, 12 per cent). The serum BEI did not change significantly. During the days immediately after operation creatine excretion increased progressively so that by the fourth day postoperatively the excretion was approximately four times the preoperative average indicating increased thyroid activity.

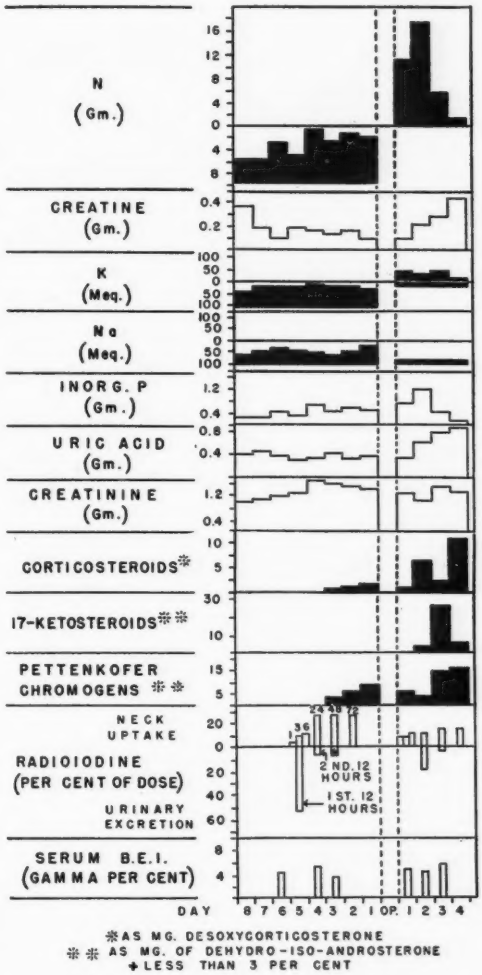

Fig. 3. Patient D.M. Data as in Figure 1.

Adrenocortical metabolites in the urine were not changed appreciably immediately after operation, but slowly increased so that Pettenkofer chromogens were twice, and corticosteroids ten times, the pre-

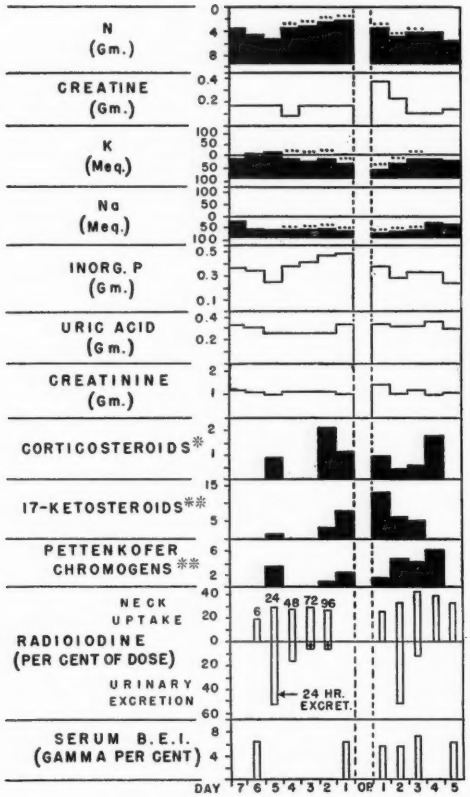

Fig. 4. Patient E.M. Data as in Figure 1.

operative levels at the end of the fourth postoperative day. The behavior of the 17-ketosteroids after operation cannot be evaluated since no preoperative determinations were available. The uric acid to creatinine ratio paralleled the increase of the hormone metabolites and at the end of the fourth postoperative day was almost three times the preoperative level. Marked sodium retention and potassium diuresis were present.

It is most important to note that a marked negative nitrogen balance which was present during the 24 hours immediately following surgery increased during the second postoperative day, but then decreased sharply so that nitrogen balance was almost restored by the fourth day after operation. During this period of decreasing levels of urinary nitrogen, adrenocortical activity was increasing rapidly and reached a peak coincidental with the restoration of nitrogen balance.

No fecal collections were made in this patient because no oral intake was planned after operation, and hence no postoperative specimen could be obtained. Progressively increasing creatinuria as evidence of thyroid activity and progressively increasing adrenocortical activity produced the net result of nitrogen balance. It can be inferred from these findings that negative nitrogen balance will persist only as long as these two endocrine glands remain in disequilibrium.

Case 4. E.M. (Fig. 4), a 36 year old female, was admitted for excision of a hard mass in the left breast which was suspicious of a cancer. Dietary equilibration was conducted for 7 days before operation. During this period the serum BEI levels remained near 6 gamma per cent and 45 microcuries of radioiodine orally administered was concentrated normally by the thyroid gland (29 per cent at 24 hours). Creatine excretion of 0.1 to 0.2 gram daily was present as was also a positive nitrogen balance. Urinary metabolites of adrenocortical hormones were fairly constant and the uric acid to creatinine ratio was between 0.25 and 0.3. In a similar fashion, the remaining urinary constituents determined were not abnormal.

Frozen section of the breast mass, 6 by 5 centimeters in diameter, revealed no cancer to be present, and complete local excision was carried out. Increased concentration of 49 microcuries of I^{131} orally administered 24 hours after surgery was evident during each counting period and reached a peak 48 hours after administration (15 per cent greater than the preoperative test at this time). Serum BEI levels remained significantly unchanged postoperatively although at 96 hours after operation (coincidental with the highest I^{131} concentration) the level had risen to 7.1 gamma per cent. Creatine excretion was double the preoperative amount 24 hours after operation indicating increased thyroid activity, but fell slowly to preoperative levels by the third postoperative day.

Pettenkofer chromogens in the urine remained static immediately after operation but slowly increased and by the fourth postoperative day were three times the preoperative levels. At this time corticosteroid excretion was also at a peak. On the other hand, the 17-ketosteroids were almost three times the average preoperative level immediately after operation and then fell to preoperative amounts by the third day after operation. The uric acid to creatinine ratio was not altered significantly by the operative stress and a slight sodium retention was evident.

It should be noted that increased thyroid activity postoperatively was paralleled by increased adrenocortical activity and during this period nitrogen excretion was essentially unchanged from the preoperative levels. Fecal nitrogen, sodium, and potassium did not change during the postoperative collection period when compared to the preoperative excretion.

CASE 5. J.A. (Fig. 5), an 18 year old female, sought therapy because of a large tibial spur which interfered with walking. It was believed that this patient was a good subject in which to study the metabolic response to operation in the presence of a thyroid gland whose activity had been suppressed by propylthiouracil administration. Prior to starting administration of this drug, and not shown in Figure 5, a tracer amount of radioiodine (11 microcuries) was administered orally and was concentrated by the thyroid gland in a probably low hyperthyroid range (43 per cent concentration 24 hours after ingestion) while the serum BEI was 7.5 gamma per cent. Oral propylthiouracil was then started at a daily dosage of 600 milligrams and was continued for 11 days prior to hospital admission.

At the time of hospital admission thyroid glandular concentration of 11.2 microcuries of intravenously administered I^{131} was 14 per cent after 24 hours and the serum BEI was 7.0 gamma per cent. Propylthiouracil dosage was then increased to 800 milligrams daily and was given during the 5 days prior to operation. During this period of time daily creatine excretion averaged 0.08 gram and a slightly negative nitrogen balance existed while other urinary constituents were stable including inorganic phosphorus which averaged 0.6 gram daily. The uric acid to creatinine ratio was approximately 0.33 and urinary steroid metabolites were fairly constant.

A benign bone spur was excised uneventfully and 1 hour after operation 12.7 microcuries of I^{131} were administered intravenously. A slight but not significant increase in thyroid glandular concentration was noted during the early hours after administration (preoperative: 1 hour, 11 per cent; 3 hours, 15 per cent; 6 hours, 12 per cent; postoperative: 1 hour, 13 per cent; 3 hours, 15 per cent; 6 hours, 15 per cent). Progressive increased concentration continued and reached a peak 48 hours after operation (20 per cent as compared to 14 per cent preoperatively). Propylthiouracil administration was continued during the postoperative period (800 milligrams daily) and the serum BEI did not vary significantly from the preoperative levels. A moderate increase in nitrogen excretion occurred postoperatively and reached a maximum at the same time that thyroid concentration of the I^{131} was the greatest. Creatine excretion also increased progressively after operation so that by the fifth postoperative day it was three times the preoperative average level indicating increased thyroid activity while inorganic phosphorus excretion increased 50 per cent.

It is important to note that there was increased nitrogen excretion coincidentally with the increased postoperative thyroid activity and delayed adrenocortical response. Nitrogen excretion then decreased as adrenocortical activity became prominent. By the fourth postoperative day when adrenocortical activity was reaching a maximum level and in the presence of continued thyroid hyperactivity (increased creatinuria), nitrogen excretion was almost equal to that of the preoperative period.

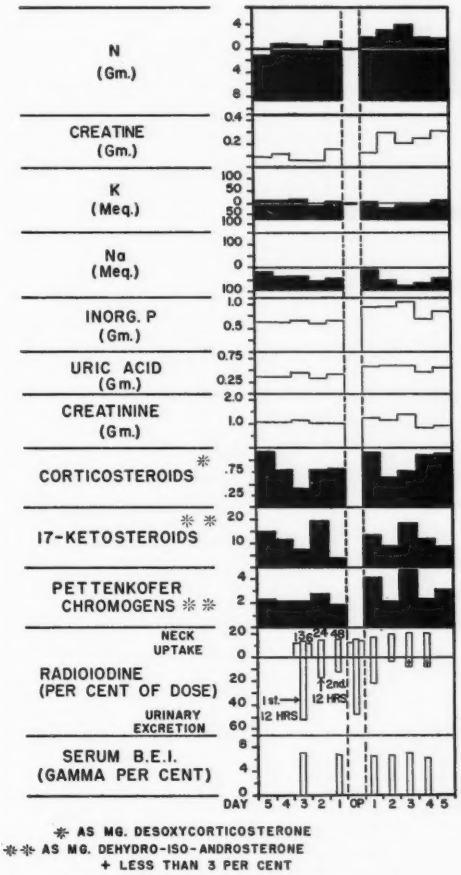

Fig. 5. Patient J.A. Data as in Figure 1.

Fecal analyses revealed no change in nitrogen, sodium, or potassium content during the postoperative period as compared to the preoperative amounts.

DISCUSSION

It is clear from the work of numerous investigators that stress produces definite metabolic alterations within the organism which disturb homeostasis. Restoration toward a steady state following trauma is controlled by the complex neuroendocrine system in which the anterior pituitary and the adrenocortical glands play key roles, but toward which the activities of the thyroid gland should be oriented. Engel believes that comparative studies

of the "metabolic effects of stress and adrenal cortical hormone overdosage emphasize the possibility that many actions that we ordinarily attribute to the adrenal hormone may in reality be induced by other stimuli, the hormone simply facilitating these reactions."

The mechanism of activation of the thyroid gland is unknown but the cerebrum, hypothalamus, and the anterior pituitary gland have all been depicted as playing important roles. The relationship of the thyroid gland to the adrenocortex is not clearly defined but studies indicate that adrenocortical hormones are antagonistic to thyroid function since thyroid activity is depressed following administration of exogenous adrenocortical hormones according to Fredrickson and Hill and their coworkers. Paschkis believes the inhibition is a direct action on the thyroid gland while Hill and his associates predicate pituitary thyrotropic stimulating hormone suppression. Histologic evidence of thyroid activation following stress has been demonstrated by Stevens and co-workers in animals in the absence of increased I^{131} concentration by the gland or increased protein-bound iodine level. The present study does not define the site of interaction since end-organ antagonism as well as direct action on the thyroid gland itself are both suggested. Failure of the BEI to rise significantly after operation in the presence of increased radioiodine concentration by the thyroid gland suggests an increased turnover of the thyroid hormone with changes in peripheral utilization rate.

The concept of inhibited peripheral utilization is strongly suggested by the data from subject E.M. in whom the initial increase in creatine excretion after operation fell sharply in the presence of increasing I^{131} concentration by the thyroid gland as adrenocortical activity was increasing. On the other hand, suppression of thyroid function at the gland itself was indicated by the decreasing radioiodine concentration by the gland (after the immediate postoperative increase) which paralleled increasing adrenocortical activity and was well illustrated in patients D.M. and S.S. It is interesting to note that patient D.M. had progressively increasing creatinuria after operation despite depressed I^{131} concentration, suggesting a dichotomy of thyroid gland activity and peripheral hormone utilization rate.

Having thus ascertained that a functional antagonism exists between thyroid and adrenocortical hormones, an attempt should be made to relate this phenomenon to the total neuroendocrine response of the organism following stress. Increased thyroid activity immediately following operation was evident in all of the patients in the present study and appeared to be the first response to the traumatic episode. With the increased metabolism thus initiated, many changes, including increased nitrogen excretion, took place. The general metabolic economy was seriously jeopardized by these changes and until readjustments were made the organism was threatened. It is here that the role of the adrenocortex becomes somewhat clearer. Increased adrenocortical activity followed the hypermetabolic derangements and initiated readjustments which counteracted the thyroid effects thus restoring a balance. It is most important to recognize that the magnitude of the adrenocortical response is directly proportional to the amount of thyroid activation. Patient, E.McC. who had only a small amount of thyroid tissue activated postoperatively displayed only minimal adrenocortical counteraction, while patient D.M. who had a pronounced thyroid effect after operation had a marked adrenocortical response which restored the steady state. It should be noted that the increased thyroid activity seen in the present series might have been more pronounced in patient D.M., if the radioiodine had been given immediately after operation instead of 24 hours postoperatively. By the time the I^{131} was given partial suppression of thyroid activity already may have been established by the adrenocortex.

Increased thyroid activity as the immediate response to stress perhaps can explain the so-called "thyroid crisis" or "storm" which has been described by McArthur and his associates as decompensated thyrotoxicosis and may be initiated by trauma such as operation (including nonthyroid procedures), infection, fatigue, and even psychic stimulation. From the data presented in the present report, it is reasonable to assume that stress causes an

increased thyroid activity which is superimposed on an already hypermetabolic state. Adrenocortical response follows, but is inadequate to counter the very high level of metabolism present so that the normal antagonistic effects to restore balance are absent and "crisis" follows. Corroboration of this postulate is present in reports of McArthur and Szilagyi and his associates where adrenocortical hormones and ACTH were beneficial in cases of "storm."

One of the most important effects of thyroid-adrenocortical antagonism in maintaining metabolic equilibrium following stress is that on nitrogen metabolism. An increase in nitrogen excretion from increased catabolism and associated with increased thyroid hormone has been reported following stress. It has been noted also that surgical patients who showed evidence of markedly increased thyroid activity after operation had a greater negative nitrogen balance than others in the same series. The significance of this hormonal antagonism is evident in patient S.S. in whom increased thyroid activity postoperatively which would probably have led eventually to marked negative nitrogen balance was promptly checked by increased adrenocortical activity and nitrogen balance was maintained. The nitrogen-sparing effect of adrenocortical products on thyroid-induced nitrogen loss was also seen in patients D.M. and E.M. in whom increased thyroid activity was associated with increased nitrogen excretion which rapidly decreased as adrenocortical activity became prominent.

It may be postulated that negative nitrogen balance does not of necessity follow operation. Rather it represents a disequilibrium between thyroid and adrenocortical activity and probably many other unknown factors. In other words, the patient with an unresponsive adrenocortex or inadequate adrenocortical reserve cannot overcome the stress induced thyroid effect and consequently enters a phase of negative nitrogen balance.

Although it has been demonstrated by Sutherland and associates that prolonged administration of propylthiouracil does not induce a hypometabolic state in a euthyroid individual, in patient J.A. it was hoped to partially block any increased thyroid activity which might follow operation. Careful evaluation of metabolic alterations could then be made in the presence of suppressed thyroid function and normal adrenocortical activity. Despite the evidence of lowered thyroid function (decreased preoperative I^{131} concentration by the gland) indicating a blocking effect of the propylthiouracil, surgical trauma still caused an increase in thyroid activity. This was demonstrated by the increased concentration of radioiodine and increased excretion of creatine after operation. Apparently the thyroid gland was partially blocked by the propylthiouracil but was still able to respond to the stressful situation with increased activity. Increased nitrogen excretion paralleled the increased thyroid activity and this was followed by increased adrenocortical function which in turn was coincidental with decreasing nitrogen excretion. The concept developed in the present investigation was thus substantiated.

This investigation makes it very clear that no constant adrenocortical response is present in any group of human subjects following stress. This may reflect either the great variability which is present in this sphere or it may be the result of incomplete determination of all of the urinary elements of steroid metabolism. The total store of knowledge regarding adrenocortical function is small and a full understanding of the complicated functions of this gland must await elucidation of the physiologic and chemical factors involved.

CONCLUSIONS

1. The response of the human to stress is mediated by a functionally integrated neuroendocrine system.

2. One of the important participants in this system is the thyroid gland, and many of the effects formerly thought to be solely adrenocortical in origin are the result of thyroid-adrenocortical interaction.

3. The immediate response to stress appears to be increased thyroid activity which causes many metabolic alterations. This is followed by increased adrenocortical activity antagonizing the thyroid effects and restoring homeostasis at a new level of metabolic requirements.

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PHYSIOLOGIC AND METABOLIC CHANGES DURING AUTOGENOUS LOBE OXYGENATION WITH TOTAL CARDIAC BY-PASS EMPLOYING THE AZYGOS FLOW PRINCIPLE

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THE demonstration that dogs will uniformly tolerate without discernible sequelae the complete occlusion of both venae cavae for 30 minutes provided that the amount of blood flowing through the azygos vein under these conditions of inflow occlusion is permitted to enter their right atrium has been termed "the azygos flow principle." This azygos vein flow, with the inferior vena cava occluded at the heart and with the superior vena cava occluded just cephalad to the azygos vein orifice, has been measured directly and found to amount to approximately 10 per cent of the normal resting cardiac output, exclusive of the coronary sinus return. These quantitative azygos flow studies have been the subject of a previous report (3).

By employing this azygos flow principle, a method has been developed which will permit intracardiac procedures in the open heart under direct vision. Essentially this has entailed the use of two extracorporeal circuits equivalent to the systemic and pulmonary circulations, each consisting of a short length of inexpensive plastic tubing (Fig. 1). The blood is massaged along synchronously and in a pulsatile stream in each of these two circulations by the multiple metal fingers of a single pump of the cam principle type (Fig. 2). Since the amount of blood flow during perfusion is quantitatively reduced to the azygos flow levels, a single lobe of autogenous lung has functioned efficiently for respiratory exchange. In 50 consecutive dogs subjected to total cardiac by-pass for varying time intervals by this method, 45 (90 per cent) were long term survivors. A more detailed description of this method has been reported recently (4).

The present study concerns the physiologic and metabolic effects of complete cardiac by-pass (complete occlusion of both venae cavae) for a period of 30 minutes during which time the circulation to the heart and vital centers of the body has been maintained by mechanical perfusion at a rate of approximately 10 per cent of the normal resting or basal cardiac output and with the employment of an autogenous lobe as the oxygenator.

OBSERVATIONS

A number of physiologic observations were made before, during, and after the 30 minute period of cardiac by-pass. These are listed as follows, and the results are summarized in Table I: (1) blood pressure (femoral); (2) plasma hemoglobin; (3) clotting time; (4) hemoglobin and hematocrit; (5) blood urea nitrogen; (6) oxygen content (blood); (7) carbon dioxide content (plasma); (8) blood *p*H; (9) lactic acid (blood); (10) bromsulphthalein excretion.

SYSTEMIC BLOOD PRESSURE DURING CARDIAC BY-PASS

The mean systemic blood pressure was recorded in the femoral artery during cardiac by-pass by employing a mercury manometer. This pressure ranged between 30 and 40 millimeters of mercury. This level of systemic pressure correlated closely with that recorded

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TABLE I.—CHANGES DURING AND AFTER 30 MINUTES OF TOTAL CARDIAC BY-PASS WITH AUTOGENOUS LOBE OXYGENATION (MEAN FIGURES)

Time	Oxygen content vols. per cent (24)		Coefficient of oxygen utilization (24)	Arterial plasma CO_2 content vols. per cent (16)	pH arterial (9)	Hemoglobin grams per cent (12)	Lactic acid mgm. per cent (2)	Plasma hemoglobin mgm. per cent (8)
	Arterial	Venous						
Preperfusion	18.4	12.5	32	36.0	7.46	13.8	14.02	6.5
At conclusion of 30 min. perfusion	21.9	3.0	86	28.8	7.11	16.5	45.37	72.0
½ hour after ending perfusion	....	....	..	33.5	7.25	15.9	31.5	....

Numbers in parentheses indicate number of animals on which means are based.

in the azygos flow study during which an equivalent amount of blood entered the heart from the azygos vein while the venae cavae were occluded. However, during cardiac by-pass with the pump in operation, the systemic arterial blood pressure tended to remain more sustained than in the azygos study, seldom being under 25 millimeters of mercury even at the end of the 30 minute perfusion. Return to control levels occurred within 1 to 5 minutes after release of the venous inflow.

INCIDENCE OF HEMOLYSIS

Plasma hemoglobin estimations were done prior to and at the end of the 30 minute perfusion period in order to gauge the hemolysis incurred during perfusion. In a series of 8 animals, the plasma hemoglobin ranged from 35 to 90 milligrams per cent with a mean value of 72 milligrams per cent. These values are well within the range of safety, for it has been demonstrated that levels well in excess of 200 milligrams per cent are necessary to produce renal damage. Such levels of hemolysis as did occur may also be considered in the light of the oft demonstrated fact that canine red cells are more easily hemolyzed than those of human blood.

USE OF ANTICOAGULANTS AND EFFECTS ON CLOTTING TIME

Because of the small amounts of blood (less than 60 c.c.) in the extracorporeal circuits as well as the comparatively rapid flow in these circuits, only minimal amounts of heparin were required to prevent clotting. By repeated trial we arrived at the dosage of 0.75 milligram per pound of body weight. The Lee-White clotting level, employing this dosage, ranged around the upper limit of normal, i.e. 10 to 15 minutes. Troublesome oozing from cut surfaces was unusual, and in the few instances in which it did occur was readily controlled with a single dose of 50 milligrams of protamine sulfate. In no instance did clotting occur in the pump circuits.

ALTERATIONS IN HEMOGLOBIN AND HEMATOCRIT LEVELS

In 18 of the animals both hemoglobin and hematocrit estimations were carried out before, during, and after the period of caval occlusion with cardiac by-pass. In most instances during the by-pass period there occurred a moderate degree of hemoconcentration as shown by the parallel rise in both estimations. These increases were of a magnitude 5 to 20 per cent over the initial control values. However, following release of the venous inflow after the 30 minute by-pass period, this hemoconcentration tended to correct itself. In some instances, within 15 minutes after normal circulation was restored, the hemoconcentration had regressed and the determinations were near the control levels. In others, the return toward normal hemoglobin levels took considerably longer.

EFFECTS ON RENAL FUNCTION

No evidence of renal damage could be detected by means of the blood urea nitrogen estimations drawn before the procedure and 24 to 48 hours after surgery. Additional determinations were carried out 3 to 4 weeks postoperatively when the animals were sacrificed. All determinations were within normal range.

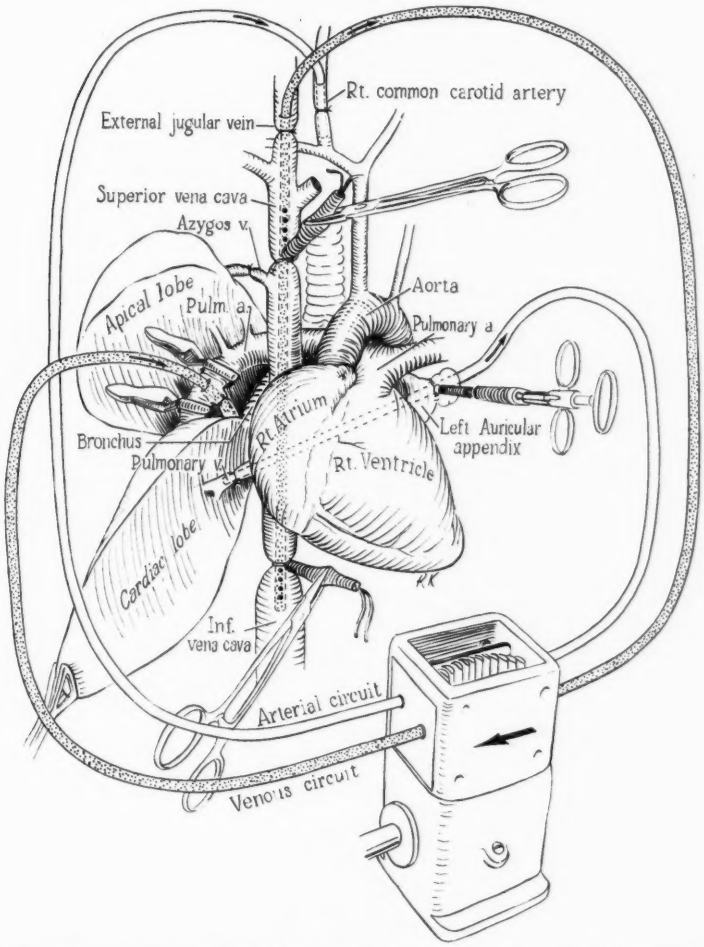

Fig. 1. Diagram showing method of total cardiac by-pass with autogenous lobe oxygenator.

BLOOD OXYGEN CONTENT DURING TOTAL CARDIAC BY-PASS

In 24 animals determinations of oxygen content in both arterial and venous blood were carried out in an attempt to estimate the efficiency of the autogenous lobe as an oxygenator under conditions of perfusion. In every instance arterial oxygen saturation was between 90 and 100 per cent as determined from a comparison of the actual content measured, with the highest possible content as calculated from the hemoglobin concentration (1.34 c.c. oxygen per gram of hemoglobin). In those instances in which hemoconcentration was fairly marked (an increase of 15 to 20 per cent over the control sample), the oxygen content rose correspondingly so that the 30 minute arterial gas analysis revealed an oxygen content of 23 or even 25 volumes per cent.

Thus, this moderate hemoconcentration became advantageous in that a greater volume of oxygen per cubic centimeter of blood was delivered to the tissues.

Another notable finding was the extreme desaturation of the venous blood returning to the venae cavae during the latter half of the 30 minute perfusion period. The mixed venous blood in the venae cavae prior to perfusion averaged 12.5 volumes per cent of oxygen in 24 dogs. At the conclusion of the 30 minutes of total cardiac by-pass the average mixed caval blood contained only 3.0 volumes per cent. These values indicate that under these conditions of reduced blood flow there has been a substantial increase in the coefficient of oxygen utilization, i.e. an increase in the quantity of oxygen extracted from a given volume of blood.

ACID-BASE BALANCE DURING CARDIAC BY-PASS

The nature and the severity of the acid-base changes occurring during the perfusion period were estimated on the basis of simultaneous plasma carbon dioxide, blood *p*H and lactic acid determinations. The mean values for these various determinations are shown in Table I. As indicated by the combined fall of carbon dioxide content of the plasma and blood *p*H, an acidosis of a metabolic nature occurred during the 30 minute perfusion period. With knowledge of the *p*H values and the carbon dioxide content, the carbon dioxide tension of the arterial blood was calculated by the Henderson-Hesselbalch equation or its normogram. A typical example may be derived as follows:

e.g. Dog 1839

	*p*H
Before perfusion	7.39
At end of 30 min. perfusion	7.04

Plasma CO_2 content

47.5 vols. per cent or 21.6 mM.L.

33.4 vols. per cent or 15.1 mM.L.

$$pCO_2 = \frac{\text{Total } CO_2}{.03\,(10^{pH-pK}+1)}$$

$$pCO_2 = \frac{21.6}{.03\,(10^{7.39-6.1}+1)} = \frac{21.6}{.03(10^{1.29}+1)} = \frac{21.6}{.03 \times 20} = \frac{21.6}{.6} = 36 \text{ mm. Hg before perfusion}$$

$$pCO_2 = \frac{15.1}{.03(10^{7.04-6.1}+1)} = \frac{15.1}{.03(10^{.94}+1)} = \frac{15.1}{.03 \times 9.5} = \frac{15.1}{.285} = 52 \text{ mm. Hg at end of 30 min. of perfusion}$$

Thus, it may be seen that the rise in carbon dioxide content tension in the arterial plasma will account for only a relatively minor part of the observed *p*H drop; the principal portion of the acidosis appeared to be the accumulation of acid metabolites which monopolized the blood buffers. This conclusion is evidenced indirectly by the drop in total carbon dioxide content, and more directly by the lactic acid rise of almost 3 times the control value (Table I).

The presence of a metabolic acidosis is not surprising and is undoubtedly in part related to a depression of kidney function during perfusion. This depression is probably the result of the low arterial blood pressure and the stasis and congestion in the inferior vena cava resulting from its cross clamping at the heart. As a result, accumulation of acid metabolites occurred, and resulted in the lowering of the blood *p*H. The carbon dioxide content and the *p*H values of the arterial blood measured at 30 minutes after the conclusion of perfusion indicated a partial return toward control values. The degree of return at this time was usually relatively small and quite likely indicated a restoration of the respiratory component of the acidosis; the major portion, or the metabolic component, required several hours or more to be eliminated.

EFFECTS OF BY-PASS ON LIVER FUNCTION

Utilizing the bromsulphalein dye retention as a test of liver function, determinations were made in 5 animals 24 hours after the period of cardiac by-pass. As controls, 5 normal dogs not operated upon, and 5 dogs which had had an abdominal operation under the same anesthesia 24 hours previously (e.g. Heidenhain pouch) were used. All of these animals (perfused, control operation, and normal not operated upon) had a normal dye retention at the end of 45 minutes (less than 10 per cent retention). It should be pointed out, however, that in 3 of the 5 perfused animals studied, the 30 minute samples showed higher levels than their controls (although all were still within the range considered normal).

DISCUSSION

The method of cardiac by-pass upon which these studies are based and the important

aspects in which it differs from others have been discussed previously(4). It has seemed to us that the keystone to success in the development of a safe and reliable method for intracardiac surgery is greater simplicity. The simplified technique herein employed for total cardiac by-pass is probably the most important single factor responsible for the high survival rate experienced in these studies. The foregoing data have served to define the nature and extent of the effects which these simplifications have had upon vital physiologic processes. Likewise, a more comprehensive understanding of the adaptive mechanisms responsible for survival under these conditions of reduced blood flow might be expected to suggest even further reductions in the complexities of achieving safe total cardiac by-pass for the performance of intracardiac surgery.

These studies are by no means comprehensive, but rather constitute a preliminary survey. Much further work is necessary to define the optimum level to which blood flow may be reduced and still maintain maximum safety. However, sufficient information has now accumulated to indicate that attempts to by-pass the heart with maintenance of a full basal cardiac output probably constitute an extravagant luxury, inasmuch as experiments now in progress indicate that ventricular and auricular cardiotomies, together with removal and suture of portions of the ventricular septum, are well tolerated by the heart under these conditions of reduced flow.

The adaptive factors permitting dogs to survive without detectable ill effects for 30 minutes with a 90 per cent reduction in their cardiac output have been discussed in an earlier report(3). Briefly, these mechanisms are a reflection of both physical and chemical phenomena (regional vasodilatation, accumulation of chemical products of metabolism, alteration of *p*H, release of epinephrine, change in tissue oxygen tension, decreased cardiac work) all of which result in a relative increase in blood flow and oxygen release to the heart and other vital centers.

In the present study, other compensatory factors of importance have become apparent. It has become evident that it is difficult to

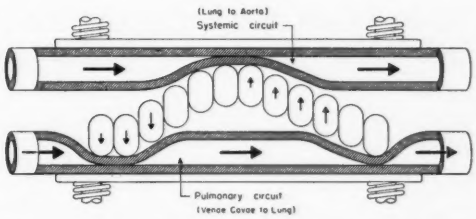

Fig. 2. Diagram showing action of metal finger pump simultaneously activating the two pump circuits.

surpass the efficiency of an autogenous lung as a medium of respiratory exchange. As an oxygenator, saturation was almost invariably 100 per cent (Table I) despite the fact that venous samples were well depleted of oxygen upon being delivered to the autogenous lobe from the venae cavae (due to the increased coefficient of oxygen utilization). The increase in the oxygen carrying capacity of the blood due to a hemoconcentration, and in the coefficient of oxygen utilization, as well as the efficiency of the autogenous lobe in readily oxygenating the desaturated venous blood, all constituted valuable compensatory factors which allowed, under these conditions of reduced flow, a given volume of blood to deliver a substantially increased quantity of oxygen to the tissues.

As indicated earlier, the occurrence of an acidosis which was almost entirely of metabolic origin rather than respiratory, again was an indication of the ability of a single autogenous lobe efficiently to eliminate carbon dioxide. A mean increase of the carbon dioxide content of 16 millimeters of mercury is a negligible consideration in terms of acid-base balance. Beecher, Miller, and others have pointed out that changes of many times this magnitude are frequent if not constant occurrences during routine thoracotomy in clinical cases. Also, the occurrence of a moderate degree of a metabolic acidosis, as observed in these experiments, may be beneficial because of the beneficial effect of lowering of *p*H upon accelerating the dissociation of oxyhemoglobin in the tissues.

A notable and gratifying feature of these studies was the absence of morbidity and mortality resulting from infection. Nelson, Spreng, and others have described the fre-

quent occurrence of paracolon bacteremia in their earlier published studies on artificial pump oxygenation with combined heart-lung by-pass. A syndrome characterized by shock, hemorrhage in the serous membranes, gastrointestinal bleeding, with incoagulability of the blood and early death, was seen to occur in a significant number of animals in which the function of both the heart and lungs was artificially maintained. In the 24 animals perfused in this study the syndrome was not encountered, in spite of the fact that these animals were perfused by using clean, but not sterile, techniques to facilitate the gathering of physiologic data. Antibiotics consisting of 600,000 units of penicillin and 1 gram of streptomycin were administered routinely postoperatively daily for 5 to 6 days. Aside from a few superficial wound infections, no untoward effects due to sepsis were noted. All animals were observed for a period of 3 to 5 weeks before sacrifice and autopsy. In only 2 animals of another series subjected to cardiac by-pass by the same method, for the performance of intracardiac procedures, 2 loculated empyemas occurred; however, a transsternal incision had been employed in these animals.

These observations with respect to infection constitute a most convincing demonstration of the vital function of pulmonic tissue in filtering out of the blood stream bacteria as well as other undesirable particulate matter such as fibrin or platelet thrombi. This fact may well constitute another distinct advantage of pulmonary tissue over methods of artificial oxygenation. These important defense functions of the lungs have been well documented by previous investigators. Beland, Moe, and Visscher have indicated a protective filtering action of lung tissue in removing harmful particulate chemical substances employed in conjunction with an isolated heart preparation. Robertson has made similar observations. More significantly, Hopkins and Parker have extensively studied the phagocytic activity of the lung in cats following the injection of streptococci. From their observations they likewise conclude that the lung was the most rapid and efficient bacterial filter, followed by liver and spleen, and finally muscle. Although the respiratory portion of the lungs in man is estimated to have an epithelial surface of 55 square meters, the capillaries in this respiratory portion have a surface area of 140 square meters. The filming of relatively small amounts of blood over a large surface area not only permits efficient respiratory exchange, but may well facilitate the trapping and phagocytosis of bacteria and minute thrombi. Finally, it is recognized clinically that the presence of septal defects associated with venoarterial shunts permits a direct shunting of particulate matter and bacteria to the systemic circulation. This phenomenon, with resultant brain abscess, has been second only to bacterial endocarditis as a cause of death in those instances of congenital heart disease associated with such shunts whereby all of the venous blood does not pass through the lungs.

SUMMARY AND CONCLUSIONS

1. Twenty-four dogs were subjected to 30 minutes of total cardiac by-pass employing mechanical perfusion and an autogenous lung lobe as the oxygenator.

2. The quantity of blood perfused through the lung lobe and pumped into the aorta for support of the dog during this 30 minute by-pass period was reduced to the azygos flow level of 8 to 14 cubic centimeters per minute per kilogram of body weight. This amount of blood constitutes approximately 10 per cent of the normal canine basal or resting cardiac output.

3. The physiologic alterations occurring in the blood pressure, red cell count, plasma hemoglobin levels, kidney and liver function, and respiratory exchange were measured during and after 30 minutes of total cardiac by-pass, and compared with control values.

4. The principle physiologic occurrences during the period of perfusion at reduced flow were moderate hemoconcentration, maximal hemoglobin saturation, marked venous desaturation, and increased coefficient of oxygen utilization. There were no significant disturbances in renal or liver function.

5. The observed metabolic effects were a moderate acidosis, of which by far the major component was metabolic. The slight eleva-

tion in carbon dioxide tension in the arterial blood was comparatively not significant.

6. The importance of autogenous pulmonary tissue as a defense mechanism against infection and harmful particulate thrombi is emphasized.

ADDENDUM: The validity of the "azygos flow concept" that complete cardiac by-pass may be performed with safe maintenance of the organism by relatively small systemic blood flows seems confirmed for man by our first clinical experience. A large interventricular septal defect was exposed by a right ventricular cardiotomy and the defect closed by interrupted silk sutures placed under direct vision. The operation and immediate postoperative period have been uncomplicated.

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PRIMARY CARCINOMA OF THE GALLBLADDER

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PRIMARY carcinoma of the gallbladder continues to be among the most uniformly lethal tumors to which man is heir. Reports compiled from numerous clinics through the years have shown little change in the overall picture. It is still very unusual for a patient having this disease to survive 5 years. As in all cancers, the feeling exists that if the lesion could be diagnosed earlier, the end results would be better, but study of these cases shows that at present we have no diagnostic means that would allow us to alter our end results materially. When confronted with this tumor the present day physician has little more to offer than did his predecessors. In the hope that further study of this problem may reveal some finding that may help in the care of these patients in the future the following series is reported. In general these cases follow the same pattern as those of previous reports. This study was made from all the patients admitted to the surgical service of the Hospital of the University of Pennsylvania between January 1940 and December 1952, inclusive, among whom 45 cases were found.

INCIDENCE

During the 12 year period of this study 2,826 gallbladder specimens obtained at operation were submitted to the Laboratory of Surgical Pathology. Among these were 44 primary carcinomas of the gallbladder. One patient in this study was not subjected to operation. The incidence generally reported is about 1 per cent of those patients submitted to biliary surgery. In different series, it has varied from 16.0 to 0.71 per cent, but in view of the fact that many gallbladders containing stones are never removed, and very few containing tumors remain undiscovered, it is likely that the true relationship of tumors to cholecystic disease is less than usually reported. Comfort, Gray, and Wilson followed 112 patients with asymptomatic gallstones for at least 10 years, during which time none developed carcinoma of the gallbladder. In the report of Donald and Fitts from this clinic, 106 patients having cholecystostomy without cholecystectomy were followed for a minimum of 10 years and none of these developed primary carcinoma in the gallbladder. In the series reported in this paper, however, 7 patients had previously had a cholecystostomy —in 1 case 45 years before. A longer follow-up period might have revealed the development of carcinoma in some of Donald and Fitts' patients. According to Arminski's collective review, the average incidence of primary carcinoma of the gallbladder at postmortem examination in this country is 0.36 per cent. He found it to comprise 4.53 per cent of all cancers found at autopsy. These figures are based on reports going back many years whereas the reports from more recent years tend to show a lower incidence. In earlier years statements can be found to the effect that deaths from cancer of the gallbladder are as infrequent as deaths from cancer of the breast and twice as frequent as deaths from carcinoma of the rectum. Such statements can hardly be given credence today and the Bureau of Census figures on which they were based were obviously misleading. The true incidence is unquestionably very difficult to determine, and in recent years the incidence seems to be decreasing when compared to operations on the biliary tract. This fact may be explained in two ways, namely: (1) the true incidence is decreasing as more gallbladders are being removed for stones, and (2) operations on the biliary tract are more common and, therefore, the ratio of tumor to operation is less. There probably is some truth in both statements.

ETIOLOGY

The etiology of carcinoma of the gallbladder is still not well understood but there seems to

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be little question of its frequent relationship to gallstones. In most tumors several factors are probably working concomitantly before malignant changes appear and gallbladder carcinomas are presumably no exception. Experimental attempts to produce tumors by introducing gallstones into healthy gallbladders have not generally been successful and certainly the vast majority of people developing gallstones do not develop cholecystic carcinomas. Constant and repeated irritation, however, has been shown many times to potentiate carcinogenic effects in animals, and it is reasonable to presume that it may in humans. The early attempts of Kazama and of Leitch to produce cancer by introducing foreign bodies into the gallbladders of guinea pigs were reported as successful in a significant proportion of their animals but a later review by Burrows cast doubt on their conclusions for he believed that not true carcinomas but rather epithelial hyperplasia were produced. More recently Petrov and Krotkina were able to produce carcinoma with metastases by the introduction of foreign bodies into the gallbladder of guinea pigs. In some they used glass rods containing radium, while in others glass alone was used. Five out of the original 100 animals developed this tumor but only after a minimum of 14 months. In only 2 of the 5 was radium used. Inasmuch as spontaneous carcinoma of the gallbladder to our knowledge has not been reported in guinea pigs, these results would appear to be quite significant and indicate that the presence of a foreign body may occasionally produce cancer in an animal that does not ordinarily develop cancer in this site.

Since some of the constituents of gallstones are chemically related to some of the most powerful of the known carcinogenic agents, the question naturally comes up as to whether or not gallstones per se are carcinogenic. The same is true of certain constituents of bile. Twenty methylcholanthrene, one of the most potent carcinogens known, is readily derived from desoxycholic acid and also from cholic acid. Cholesterol, which forms the basis of most stones, is likewise related chemically to the carcinogens but so far as they have been compared with other inert foreign bodies, gallstones do not seem to have any specific carcinogenic effect related to their chemical composition. The work of Desforges and associates is interesting in this regard. They were unsuccessful in their attempts to produce this tumor in guinea pigs when they introduced glass beads, cholesterol pellets, and even 5 per cent 20 methylcholanthrene pellets. It is quite possible, however, that their period of observation (9 months) was insufficient, and had this period been doubled or tripled they might well have seen a significant number of tumors particularly among the later group in which only proliferative changes were found. Certainly from this work it does not appear that the biliary tract is readily susceptible to carcinogenesis. Such conclusions tend to be borne out by the fact that less than 2 per cent of patients having gallstones develop this form of carcinoma.

TABLE I. — SIGNS AND SYMPTOMS

	No. of cases	Per cent
Weight loss	38	85
Pain	35	78
Nausea	22	49
Jaundice	21	47
Profound weakness	13	29
Painless jaundice	9	20
Tarry stools	1	2
Liver palpable	30	67
Mass palpable other than liver	24	53

Sex. In this series of 45 cases there were 34 women and 11 men, a ratio of roughly 3 to 1. This is approximately the same ratio that is seen in gallbladder disease generally.

Age. The increased incidence of cancer of the gallbladder in the older age groups is readily seen in this series as it is in others: aged 40 to 49 years, 2 cases; 50 to 59 years, 10 cases; 60 to 69 years, 22 cases; 70 to 79 years, 9 cases; 80 to 89 years, 2 cases. The maximum incidence is in the seventh decade. The extremes of age were 40 and 88 years.

Signs and symptoms. The presenting signs and symptoms were quite variable but some were repeatedly encountered. Of the 45 patients, 35 or 78 per cent complained of pain in the region of the gallbladder, while the remain-

TABLE II.—DURATION OF SYMPTOMS OF GALLBLADDER DISEASE

	No. of patients	Per cent
More than 5 years	16	36
One to 5 years	6	13
One month to 1 year	14	31
Less than 1 month	8	18
Undetermined	1	2

ing 10 had no pain. In many the pain had become constant by the time of their admission to the hospital. Nausea too was frequently experienced. It was found in 22 or approximately 50 per cent of the patients. Weight loss was the most constant finding and was present in 38 patients. This varied from rather small amounts to 50 pounds. The majority of patients lost more than 10 pounds. Profound weakness was a prominent complaint in 12 patients.

Jaundice was present in 21 patients at the time of admission and in 9 of these patients it was painless. Although painless jaundice is often associated in our minds with pancreatic tumors, one should not overlook the possibility of primary biliary duct or gallbladder cancer being the source of such a condition when it is encountered.

Hepatic enlargement was found in 30 of the 45 patients, and an additional mass in the region of the gallbladder was felt in 24. In 1 patient the tumor was actually fungating through the skin of the abdomen. Table I summarizes these findings.

Of considerable interest was the fact that 18 patients had noticed a recent distinct change in their old symptoms of gallbladder disease. The change in symptomatology was no doubt due to a change in the fundamental disease giving rise to it, that is, the development of carcinoma in the gallbladder containing stones.

The duration of symptoms of gallbladder disease prior to admission to the hospital was also of interest. It was very variable as one would expect, and many had had symptoms of gallstones for years. These are the patients who presumably could have been prevented from developing tumors had cholecystectomy been carried out when first the symptoms of gallbladder disease appeared. Table II summarizes the findings in this regard.

The shortest period during which a patient had symptoms was 9 days and the longest was 45 years.

The preoperative diagnosis varied greatly but in 11 the diagnosis of carcinoma of the gallbladder or biliary tree was made correctly, and in an additional 8 patients some form of abdominal carcinoma was suspected. Chronic cholecystitis was diagnosed 11 times, acute cholecystitis 6 times, common duct stone 3 times, and "obstructive jaundice" 5 times.

TREATMENT

Forty-four of these 45 patients were subjected to laparotomy and at operation only 5 were found to have a lesion that the surgeon considered possibly curable. In all others it was believed to be clearly incurable. Of these 5 patients 1 has apparently been cured and is alive and well 11 years later. She had a small tumor that was found incidentally in a hydropic gallbladder containing stones. The other 4 have all died, the longest survival being only 2 years. The operative procedures carried out included: cholecystectomy (with hope of cure) in 5 cases; cholecystectomy (palliative only) in 9 cases; cholecystostomy in 14 cases; biopsy only in 10 cases; choledochostomy in 10 cases; radical excision (right colectomy, partial hepatectomy and gastrectomy) in 1 case; no operation in 1 case. It should be pointed out that in a few patients choledochostomy was done with cholecystectomy or cholecystostomy so that the total number of procedures appears greater than 44.

GALLSTONES

In this series, biliary calculi were found at some time in 33 patients or 73 per cent. In 9 patients or 20 per cent, the presence or absence of stones was never definitely determined and in the remaining 3 or 7 per cent, stones were clearly absent. Occasionally, even at operation, one could not be certain if stones were present since the tumor was too extensive to warrant resection or permit adequate palpation. In Arminski's review of over 2,000 cases 73.2 per cent were known to have stones.

In the study of these cases a few interesting facts were disclosed. Seven of these patients had previously been subjected to cholecystostomies, several more than 15 years before, and 1, 45 years previously. In all but 1 of the 7 at least several years had elapsed since their operation, but in 1 case the cholecystostomy was performed only 3 months prior to admission to our hospital. It seems likely that the tumor was then present but unrecognized. Two patients (both of whom had calculi) had previously had typhoid fever.

LIFE EXPECTANCY

The almost uniformly poor results that have followed treatment of this disease have again been encountered in this series (Table III). Approximately one-half of the patients died within 3 months of their operations. There is only 1 patient who had a long term survival and she is well 11 years later. The next longest survival was only 39 months. Table III shows the postoperative survival, and one can readily see that there are few tumors whose end results are as bad. We were able to trace all but 1 of these patients and thus have followed 98 per cent. The 1 untraced patient had far advanced disease at the time he left the hospital.

PATHOLOGY

Of the 45 carcinomas in this study 39 were glandular in type, 5 were undifferentiated, and 1 was a squamous cell carcinoma. These tumors spread rapidly both by direct invasion of the liver and surrounding viscera and by lymphatic spread into the region of the hilus of the liver and thence elsewhere. The rapid spread of this cancer is evidenced by the fact that in only 5 of our cases did it appear to the operator that the tumor was not incurable at the time of surgery. In 2 of the 5 the operator was unaware of the fact that he was dealing with a carcinoma at the time he did a cholecystectomy, and only 1 of these was apparently cured. Many unusual types of spread have been reported in the literature. In this series 1 of the tumors actually fungated through the abdominal wall prior to the patient's admission to the hospital, and the superficial mass was the presenting complaint.

TABLE III. — POSTOPERATIVE SURVIVAL PERIOD

Postoperative survival	No. of patients	Per cent
0–3 months	20	45
4–6 months	5	11
7–12 months	11	24
1–2 years	3	7
2–3 years	1	2
3–4 years	2	4
Over 4 years	1	2
Undetermined	1	2
Unoperated (died within 3 weeks of admission)	1	2

DISCUSSION

Few, if any, tumors carry a worse prognosis than does carcinoma of the gallbladder, and it would seem unlikely that we will see a significant improvement in the end results of this disease with our present means of diagnosis and treatment. We may well see a decrease in its incidence since it appears that the disease could have been prevented in approximately one-half of the cases if the gallbladder had been removed when symptoms of gallstones first developed. This fact immediately raises the question as to whether or not a gallbladder containing stones should routinely be removed as precancerous. It is our belief that the danger of malignant change is too small (probably less than 1 per cent) to advocate routine cholecystectomy for this reason alone. The risk of operation is about as great as the risk of developing cancer. Nevertheless for other reasons we strongly advocate the removal of *symptomatic* gallbladders containing stones unless there are real contraindications. There are too many other serious complications that can arise from gallstones and the combined risk is far greater than the risk of cholecystectomy. The prophylaxis afforded by cholecystectomy against development of carcinoma of the gallbladder is an added advantage. If symptomatic gallstones were routinely removed with the gallbladder we would undoubtedly reduce the incidence of carcinoma of the gallbladder as well as the other complications of gallbladder disease.

Once developed, except in its very early stages when this tumor itself is asymptomatic,

this carcinoma is usually incurable by any presently available means. Partial hepatectomy along with cholecystectomy has not materially altered the end results. This tumor invades the liver early and it rarely can be totally removed. Because of its early incurability we doubt if a greater awareness of the disease and consciousness of its symptomatology will have significant effect on its end result. Our best hope for improvement lies in prevention and not in treatment. The evil reputation of this tumor is only too well deserved.

SUMMARY

1. A series of 45 cases of primary carcinoma of the gallbladder is presented.

2. This tumor is among the most serious of all cancers and occurs in about 1 per cent of gallbladders containing stones.

3. Approximately three-quarters of these cancers are associated with gallstones.

4. Although gallstones probably contribute to tumor formation by irritation there is not good evidence that their chemical structure is of itself carcinogenic. The possibility of substances in the bile being carcinogenic, however, remains.

5. Once the tumor is symptomatic it is nearly always incurable.

6. At present our only hope for improvement in the end results lies in prevention rather than cure. More frequent cholecystectomy for symptomatic gallstones should result in a lowered incidence of carcinoma of the gallbladder.

7. Approximately one-half of the patients in this series could, no doubt, have been prevented from developing carcinoma if a cholecystectomy had been carried out when the gallstones were first symptomatic.

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INFECTION IN BURNS

I. The Problem and Evaluation of Therapy

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BACTERIOLOGIC studies in the burned patient are subject to continuous revision and redefinition as newer methods of burn therapy are projected, evaluated, and finally assigned a place in the armamentarium of medical practice. The importance of infection in the burned patient assumes different values when the occlusive pressure dressing technique or the exposure method is used: as, through improved therapy, greater insight into the water, electrolyte, and protein metabolism alters the resistance and survival of the burned patient; as early débridement becomes more widely practiced; and as each new antibiotic agent is given a trial. These and countless other developments require a continuous effort on the part of the medical profession to bring the problems of infection into sharp focus against a changing therapeutic background.

In burned patients, infection may be broadly defined as the presence of any micro-organism on the burn wound or the invasion of the body by micro-organisms. This definition deliberately includes the colonization of granulation tissue by organisms that may or may not have pathogenic potentialities. Such a broad definition is necessary since the common condition of potentially benign surface growth of bacteria on granulation tissue must be included in a consideration of infection in burned individuals. This is in harmony with Colebrook's (5) definition, "*infection* by itself is used throughout in a bacteriological rather than a clinical sense. Where necessary it is qualified by the addition of *silent*, to imply the absence of clinical signs and symptoms." Silent infection we consider equivalent to colonization. In contrast to this, Meleney prefers a definition limiting infection to "the reaction of the tissues in and about the wound to the presence of micro-organisms and their poisons."

In this consideration of the burned patient, infection is divided into three subtypes: (1) colonization, which involves organisms with or without pathogenic potentialities; (2) local invasive infection, which is characterized by local signs of inflammation; and (3) general invasive infection, which is characterized by lymphangitis, lymphadenitis, spiking fever, leucocytosis, and bacteremia. Suppuration may or may not be a feature of any of these three categories.

Recent reports on infection in burns are somewhat confusing in that they do not distinguish clearly between infectious processes during different phases of the history of the burn. Infection has an entirely different significance in the early postburn period than in the later stages: major infectious complications are a very real hazard only until the body has organized its defenses and formed granulation tissue, which acts as a remarkably effective barrier against invasive infection. In the granulating phase serious invasive infection is rarely encountered. Colebrook's (4, 5) work, which constitutes the outstanding contribution to the bacteriology of burns, does not clearly emphasize the relationship between the type of infectious complications encountered and the time of their development. A schema, which is largely self-explanatory, is presented to illustrate the infectious complications in relation to the natural history of a third degree burn (Fig. 1). The danger of invasive infection is greatest before the separation of eschars has occurred.

This series of papers deals with studies on burned patients under treatment on the Burn Service of the Surgical Research Unit. Several problems concerning infection have been

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studied, including the prevalence of early invasive infection associated with positive blood cultures, the definition of the pathogenic importance of various bacteria, and the use of various local agents in the preparation of burn wounds for closure by grafting. In this paper, the statement of the problems and the manner in which the results have been evaluated will be discussed.

The general approach in the investigative work may be considered as follows:

Source of patients. The patients consisted of members of the Armed Forces and their dependents who were admitted to Brooke Army Hospital shortly after injury. Air evacuation of these patients from various areas in continental United States was under the direct supervision of the personnel of the Unit. Personnel from overseas who required treatment were also sent to Brooke Army Hospital. With the exception of a few dependents who were treated at Brooke Army Hospital, the patients were healthy, young men under 30 years of age.

Hospital facilities. A well staffed, spacious, and well aired burn ward that can accommodate 50 patients is located on the fourth floor of the hospital. A large, well ventilated dressing room is immediately adjacent to the ward. The operating rooms are located on the adjacent floor, are air-conditioned, and have standards for the circulation and purification of air that are equivalent to those described by Bourdillon.

General plan of burn therapy. The acute burns are treated by methods described elsewhere (1, 2, 11). The most significant feature of the early treatment, differing from that used in many other institutions, is the tendency to treat the burned parts by use of the exposure method (to expose the burned parts to the air). The fluid therapy and early excision of the eschars are practiced essentially as elsewhere. It must be strongly emphasized that, after eschar removal is achieved, all full thickness burns are treated by the application of bulky, absorptive, occlusive dressings. Exposure of wounds other than recent burns is to be condemned. Wound closure by the application of split thickness skin grafts is initiated as soon as the granulation tissue is ready for grafting as judged by its gross appearance. Where motion is apt to dislodge grafts, they are sewn in place, such as in the groin region, over joints, on the hands, and on the head and neck. Otherwise, the grafts are applied to the recipient sites without suturing, and occlusive compression dressings are applied. In general, grafting procedures are well standardized so that different results in grafting can be reasonably considered a reflection of factors other than technical ones. The diet and supplements of the convalescent burn patient are designed to accomplish the optimum intake of calories, nitrogen, and vitamins; the hemoglobin and protein concentrations in the serum are supported by whole blood transfusions when indicated.

Methods of dressing changes. General anesthesia always entails certain hazards, and its frequent use reduces the food intake. For these reasons, the great majority of dressing changes are performed in the ward dressing room. The indications for a dressing change in the operating room are as follows: (1) when dressings are changed before the development of a granulating surface; eschars are commonly removed during the same procedure, and this requires anesthesia; (2) when dressings must be changed on a patient who has a burn wound of more than 10 per cent of the body surface. This necessitates the elaborate facilities of the operating room for expeditious handling, and the change of dressing requires anesthesia for the comfort and/or relaxation of the patient; and (3) when dressings are changed in conjunction with grafting procedures.

During the dressing changes, an aseptic "no-touch" technique is used. The patients and attendants are masked. Materials for the dressings and instruments are supplied either from individually sterilized packages in the operating room, or from sterilized containers when the dressing changes are performed in the ward dressing room.

Bacteriologic studies. Samples for cultures are taken from every wound at every dressing change by the use of two dry cotton swabs, which are placed in 1 cubic centimeter of a trypticase soy broth, generally within the hour. The swabs, in broth, occasionally re-

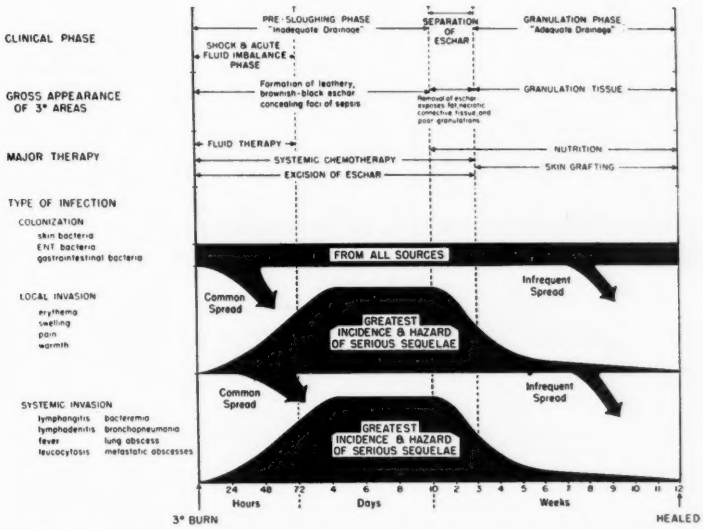


Fig. 1. Natural history of a third degree burn with survival. Note that danger of invasive infection is greatest before separation of eschars has occurred. In the presence of granulating wounds, invasive infection is rare.

main overnight in a refrigerator at 9 to 11 degrees C. before they are used to inoculate the media. One swab is used to inoculate plates of trypticase soy blood agar, milk-salt agar (essentially Chapman's salt agar made with 20 per cent evaporated milk), and phenylethyl alcohol blood agar. The other swab is placed in a tube of thioglycollate broth. The latter swab provides some degree of dilution of the initial swab soaked in the trypticase soy broth. Since specific agents to neutralize the effects of various antibiotic substances used therapeutically are not available, except in the case of penicillin, the only control obtained on the theoretically possible conveyance of the antibiotic into the culture (which might yield a falsely negative culture) is the comparison of growth on blood agar plates inoculated from the thioglycollate broth culture with that of the original blood agar plates. Dilution of the medium did not result in the isolation of additional microbes. Subcultures from the plate media were used to identify the organisms. Sensitivity to several antibiotics was determined by the filter paper disk method after the microbes had been isolated in pure culture. A smear was also made from the original swab.

There is a definite reason for using the four media mentioned. Since the burn wounds, in the large majority of cases, are colonized by a mixed bacterial flora, measures must be taken to prevent certain of the microbes from overgrowing the others. On blood agar plates, gram-negative bacilli have a tendency to grow so rapidly that, in their presence, gram-positive organisms are difficult to isolate. Media that inhibit the growth of the gram-negative bacilli must therefore be used. The milk-salt agar plates are used for detecting staphylococcus aureus. This medium is used to facilitate a special study that concerns bacteriophage typing of staphylococci in burns and will be reported at a later date. On the phenylethyl alcohol blood agar plates, the growth and swarming of gram-negative bacilli are inhibited, but gram-positive organisms grow well. Specific methods for growing anaerobic organisms have not been used routinely, but the conditions at the bottom of the thioglycollate broth tubes are nearly anaerobic, and this sometimes makes it possible to recover anaerobic organisms. Our studies are concerned principally with aerobic microbes which colonize burn wounds frequently.

Before 1951, when inhibitory media were not used by us, streptococci were recovered only rarely from burn wounds. Since that time, the aforementioned bacteriologic technique has been observed, and streptococci have been cultured much more frequently. Since 1951, micrococci as well as streptococci have been found more frequently than before. The improved culture technique appeared to be mainly responsible for these changes. Other factors that could be responsible for the presence of gram-positive cocci, such as patient material, type of burns, local care of the burn wounds, and use of antibiotics, have remained essentially unaltered.

It is recognized that these methods will not reveal all the microbes that colonize the wounds. It is believed, however, that they are adequate for rapid detection of predominant bacterial types and for the determination of antibiotic sensitivity.

The blood cultures are taken by a special technique. Face masks are used by patients and personnel. The skin is carefully prepared with tincture of iodine, and the blood is drawn with a set composed of a syringe and needle sterilized as a unit in a large test tube. Three media are then inoculated with the blood; 5 cubic centimeters of blood are injected into 45 cubic centimeters of trypticase soy broth and 5 cubic centimeters into 45 cubic centimeters of thioglycollate broth. A few drops of blood are placed directly on a blood agar plate. Penicillinase is added to the media if the patient is under treatment with penicillin. For patients receiving other chemotherapeutic agents, the dilution of 5 cubic centimeters of blood by 45 cubic centimeters of culture media is the only means used to minimize the effects of the antibiotic agent in the cultures. Admittedly, until methods are available for specifically neutralizing each antibiotic agent, such a technique for isolating bacteria may yield some falsely negative cultures. The inoculated media are incubated at 37 degrees and examined at 24 hour intervals. Smears are prepared at every examination, and organisms found are carried over to the aforementioned media, isolated in pure culture, and tested for sensitivity to several antibiotics.

Quantitation of data. Information for analysis was quantitated, as far as possible, in an effort to avoid the pitfalls of clinical impressions. Estimates of graft takes were evaluated as a percentage of the total area originally grafted. The gross appearance of the granulation tissue, amount of wound exudate, and local signs of invasive infection were noted and recorded whenever the wound was inspected. An arbitrary scale of 5 numbers was employed to grade the amount of suppuration. Usually, though not invariably, any quantitative data were evaluated by two observers, one of whom was the principal investigator, to decrease any personal bias that might have prejudiced the results.

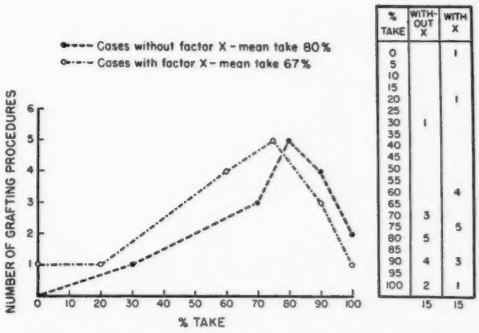
Statistical evaluation. Unless appropriate controls are used in the evaluation of topically applied agents, the conclusions are generally based on the earnest, well meaning conviction of the investigator who commonly employs his past experience as a yardstick for measuring the results. The degree and direction of bias thus introduced is unknown, but probably is rarely small.

In an effort to avoid such difficulties, patients should be used as their own controls whenever possible. This can be done in patients who have two wounds of comparable extent and location, when one wound is characterized by a particular factor that is absent from or does not influence the other. The factor affecting one wound only may be the presence of a certain microbe, an antibacterial agent, some mechanical factor, or one of many other conditions that an investigator may wish to evaluate. Fortuitously, nearly all of the patients in our studies had wounds suitable for this type of experimental design.

There is a great advantage in using paired wounds *in individual patients* for the statistical assessment of whether a particular observed difference in wounds can be validly ascribed to factors other than chance. Suppose that 30 wounds are observed in 15 patients and that each patient has 2 comparable wounds, one of which differs in some important respect from the other. If the wounds in each patient are grafted at the same time and the percentage of take is recorded for every wound, alternative approaches are available

for statistical treatment, namely, analysis of the data on graft takes in 30 wounds or 15 pairs of wounds. (1) It is possible to calculate, from 15 patients, the mean take of the 15 wounds, all of which are similar with respect to the factor under investigation, and compare this mean with the mean take of the remaining 15 wounds. This comparison may be accomplished by the "t" or "F" tests, described by Fisher, which give identical results in the comparison of two means (6). The reliability of the mean of each series is dependent on the number of observations that contribute to the mean as well as to the distribution of the data around the mean (variability): the more narrow the distribution of data around the mean, the more reliable the mean becomes. It is evident that, within each series of observations, the distribution of takes is caused by many factors other than the factor under evaluation. By the method of pairing, these factors are largely eliminated as contributing to the variability of the data, and, therefore, must not be reintroduced in the calculation of this variability. This is exactly what has been done in the aforementioned comparison of means, in which the pairs were broken up and the two series were examined separately. (2) The proper approach is to compute the difference in takes between paired wounds and, from this, the mean of differences in take. By use of the "t" test, it is then easy to calculate whether the observed mean of differences departs significantly from a value of zero, which would be expected if the factor under investigation failed to influence the results. The analysis of the difference of means (first method) and the analysis of mean of differences (method of pairing, second method) are statistical treatments that are clearly distinct and profoundly different in meaning. The distinction has been discussed elegantly by Fisher (7) and Mather. When pairs are not available for analysis, comparison of differences of means is, of course, the only method available, but the interpretation of information so derived is more restricted than that based on paired data.

Whenever possible, data should be expressed in quantitative terms. The analysis of quantitative estimates by the statistical procedure


Cases without factor X - mean take 80%
Cases with factor X - mean take 67%
NUMBER OF GRAFTING PROCEDURES
% TAKE
0 10 20 30 40 50 60 70 80 90 100
1 2 3 4 5 6

% TAKE	WITHOUT X	WITH X
0		1
5		
10		
15		
20		1
25		
30	1	
35		
40		
45		
50		
55		
60		4
65		
70	3	
75		5
80	5	
85		
90	4	3
95		
100	2	1
	15	15

Fig. 2. Hypothetical distributions of graft takes in two series of wounds, one of which is characterized by the presence and the other by the absence of a factor x. If an 80 per cent graft take is chosen as the dividing line between success and failure, chi-square is 4.8 ($P<0.05$), and there appears to be a significant difference in the percentage of take between the series. However, a dividing line of 75 per cent yields a chi-square of 0.005 ($P>0.9$), and a conclusion of a significant difference is not justified. The mean takes of the two series are 67 and 80 per cent respectively. By the "t" test, $t_{28}=1.6$ ($P>0.1$), and the difference again appears to be nonsignificant.

outlined in the preceding paragraph appears to have certain advantages over the use of qualitative statistics, in which the frequency of occurrence or nonoccurrence of a particular event is compared in a control and experimental sample. Qualitative statistics can be examined by the chi-square test, and this test was employed by Jackson and others in their excellent study on the pathogenicity of Streptococcus pyogenes in burns. In that study, a graft take of less than 80 per cent was arbitrarily defined as "failure"; a take of 80 per cent or more was defined as "success." In such an analysis, the distribution of takes is not taken into account and, consequently, a take of 79 per cent is regarded as much of a failure as a take of 0 per cent, and a take of 81 per cent is considered equivalent to a take of 100 per cent. It would appear to be preferable to determine the mean take in the experimental and control series and thus allow each grafting procedure to influence the results in proportion to its "success" or "failure." When qualitative statistics depend on arbitrary definitions, there is no assurance that some other dividing line between success and failure may not yield results of greatly different significance. In this respect, it must

be noted that qualitative statistics obscure the magnitude of the difference observed. This effect of arbitrary dividing lines is illustrated in a somewhat exaggerated form in Figure 2. It is seen that, in the hypothetic graft data presented, an 80 per cent dividing line gives a verdict of a probably significant difference between the two series ($P<0.05$). However, when an arbitrary dividing line of 75 per cent is selected, P is greater than 0.9 and significance is not established. Similarly, if the distribution of takes in each series is taken into consideration, a verdict of non-significance is reached.

The use of qualitative statistics becomes necessary, of course, when quantitation of data cannot be achieved in any way. Under these conditions, qualitative statistics are greatly to be preferred over clinical impressions that fail to take into account the extent to which sampling differences may affect the results.

SUMMARY

Bacteriologic studies in burned patients are of continuing interest because of the wide range of antibiotics available for the therapy and changing methods of local care. Infection in burns must be considered in the light of the natural history of a severe burn.

As a background for further studies, the source of patients, hospital facilities, methods of dressing changes, general plan of burn therapy, bacteriologic methods, quantitation of data, and the concepts in statistical evaluation are discussed.

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SOME HORMONAL ASPECTS OF HUMAN PARTURITION WITH PARTICULAR REFERENCE TO THE NEUROHYPOPHYSIS

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THE neurohypophysis consists of certain hypothalamic nuclei, their axons which traverse the stalk, and the posterior pituitary lobe where the axons end. The posterior pituitary must be thought of as a portion of a unit, the unit being the neurohypophysis. The posterior pituitary is considered a gland of internal secretion and upon assay of whole extracts an antidiuretic, an oxytocic, and a pressor factor are obtained.

It is not clear whether the posterior lobe contains a single hormone with multiple pharmacologic activities or two or more hormones. It is impossible by physiologic experimental stimulation of the gland to deplete one factor and leave another in situ, and experimental operations causing an atrophy of the posterior pituitary result in a loss of all excitants. A relative loss or depletion of one activity is accompanied in essence by a parallel loss of the others.

The syndrome of diabetes insipidus may be described as a polyuria of low specific gravity with polydipsia which is attributed to a deficiency of the posterior pituitary antidiuretic hormone. The etiologic factor interfering with posterior pituitary function is in many instances unknown, but may be tumor, infection, trauma, or a metabolic disease. Heredity may be a factor. Not all instances of polyuria with polydipsia are diabetes insipidus, as for example, the polydipsia may be purely on a psychogenic basis. Other physiologic defects may warrant consideration also. The data pertaining to human delivery in patients with diabetes insipidus have been clouded largely by a lack of an objective physiologic test which will confirm the validity of the diagnosis of diabetes insipidus, and by implication a neurohypophyseal lesion. In general, it is thought that the endocrine importance of the neurohypophysis in human delivery is not established. The present study is directed as an attempt toward clarification of this issue.

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ANIMAL EXPERIMENTS

The effectiveness with which extracts of the posterior lobe strengthen uterine contraction at parturition has led to speculation that the posterior lobe may play an essential role in delivery. Animal experiments are not in agreement. Smith, in a study of rats in which he removed only the posterior lobe, found the animals to have a normal sexual cycle, gestation period, and delivery. Pencharz and Long found that hypophysectomy of pregnant rats allowed for a normal parturition in the absence of the posterior lobe if sufficient anterior lobe was present, but with destruction of the anterior lobe of the pituitary, the pregnant animals had prolonged gestation periods and prolonged labors. No mention of diabetes insipidus as a concomitant finding was made in either study. Fisher, Magoun, and Ranson observed 7 pregnant cats with diabetes insipidus secondary to bilateral anterior hypothalamic lesions which interrupted the supraoptic component of the hypothalamic-hypophyseal tract. The cats were operated upon in various stages of pregnancy and 6 were totally or partially unable to deliver their young, 4 died in labor, and 2 succumbed some days later. Ingram observed 1 dog with experimental diabetes insipidus which bred and delivered her young without mishap. Lake

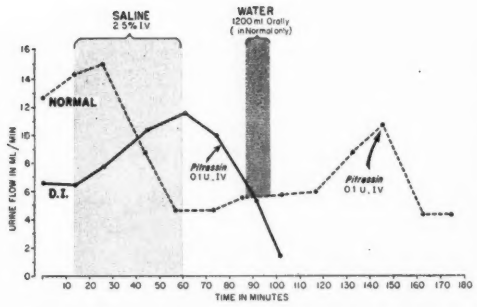

Fig. 1. Effect of hypertonic saline on urine flow in normal and diabetes insipidus nonpregnant patients. After hydration, the intravenous hypertonic sodium chloride caused an antidiuresis in the normal patient and a continued diuresis in the diabetes insipidus patient; the difference in response rests with the outpouring of antidiuretic hormone from the normal neurohypophysis. The similarity between the responses to endogenous and exogenous antidiuretic hormone is shown in the normal patient.

states that monkeys with diabetes insipidus have dystocia at the time of labor, but no reference or datum was given. Gersh studied osmiophilic cytoplasmic inclusion droplets within the posterior lobe cells at the time of parturition and following dehydration. An increased droplet content described by him represented an index of increased activity. Upon examination of Gersh's thesis with respect to the osmiophilic droplets and dehydration, it was impossible to confirm the study (6).

PATIENT MATERIAL

This study centers around the use of an objective test, which will reliably indicate true diabetes insipidus, particularly as applied to 1 patient, followed by the University clinics for 12 years. We have been able to study this patient before and during pregnancy, during delivery, and after single as well as multiple births.

P.G., 41-7914, diabetes insipidus. The patient had an acute exanthema, probably scarlet fever, at the age of 12 years with the onset of polyuria and polydipsia 2 months later. As she grew to maturity, her physical development and bodily configuration were feminine and within normal range.

Her first menstruation was at age 17 years with menstrual periods from 40 to 90 days and lasting 2 to 3 days. Her first pregnancy resulted in a normal delivery at age 19, and an uncomplicated twin pregnancy and delivery occurred at age 23 years.

As an adult her urinary output was 10 liters daily with a specific gravity of 1.001 if untreated, and when pitressin tannate-in-oil® was given normal outputs with specific gravity to 1.030 were attained. Aside from the diabetes insipidus, detailed clinical and laboratory investigations revealed no significant aberration. The skull roentgenograms were normal on repeated occasions, and a pneumoencephalogram was normal also.

C.W., 53-3594, control. This patient was a 49 year old female, an inmate of a county home, who entered upon the surgical service for a repair of a severe rectal prolapse. On clinical laboratory study no other lesion was noted. The studies were carried out preoperatively.

L.B., 53-9213, control pregnant. This patient was a 30 year old female, para 2, gravida 3, an inmate of a mental institution whose pregnancy was uncomplicated and whose physical health was satisfactory on clinical and laboratory analysis.

B.L., 53-10812, control. This patient was a 21 year old female, admitted to the hospital from a mental institution for tubal ligation. Her physical health was excellent. The studies were carried out preoperatively.

All control patients were able to concentrate and dilute urine normally, each had a normal intravenous pyelogram, and the blood urea nitrogen and blood creatinine levels were satisfactory.

THEORETIC CONSIDERATIONS

The technique for testing the functional hormonal integrity of the neurohypophysis is based on the work of Hare, Hare, and Phillips who demonstrate a consistent difference in the renal response in normal dogs and in dogs with experimental diabetes insipidus after the administration of intravenous hypertonic saline. Upon extending this work to the human (5) it was found to apply equally well, and these studies have since then been confirmed.

The difference in the test response of normal subjects and those with diabetes insipidus may be measured by changes in the chloride concentration of the tubular reabsorbate to that of the plasma chloride (R/P ratio), by changes in the urinary chloride concentration to that of plasma chloride (U/P ratio), or simply by the rate of urine flow. In response to the administration of hypertonic saline, the normal subject shows a fall in the chloride R/P ratio, while in the diabetes insipidus patient with an already elevated chloride R/P ratio, the rise is still

further. The chloride U/P ratio in the normal subject shows a sharp elevation after hypertonic saline and is not so reflected in the insipidus patient. Both the chloride R/P ratio and the chloride U/P ratio involve detailed chemical analyses with the R/P ratio requiring in addition a measure of glomerular filtration. The final indicator, that of urine flow, is easily measured and is thus of clinical advantage. The fundamental difference between the normal and the insipidus patient is attributed to the presence of circulating antidiuretic hormone. The amount of antidiuretic hormone released from the posterior lobe is increased in response to changes in blood osmotic pressure incident to the intravenously administered hypertonic salt.

METHOD

The clinical application of the differential hypertonic saline test is readily accomplished. Under basal conditions, the test subject is given water orally in the amount of 20 milliliters per kilogram over an hour's period for purposes of hydration. An indwelling catheter is inserted into the bladder during the latter half of the hydration period and two control periods of urine flow are appraised. A measurable polyuria must be obtained and this may be somewhat tardy in pregnant patients.

Measurements of urine flow are made by washing the bladder with air at approximately 15 minute intervals. At this point hypertonic 2.5 per cent sodium chloride is given intravenously for 45 minutes at the rate of 0.25 milliliters per kilogram per minute. The test is extended to cover two or more postinfusion periods and the results are analyzed graphically on the basis of urine flow expressed as milliliters per minute.

RESULTS

In the presence of an intact neurohypophysis, there occurs an outpouring of antidiuretic hormone in response to the blood osmotic changes caused by the hypertonic salt. The antidiuretic hormone acts upon the renal tubules, causing reabsorption of water, and there occurs a prompt drop in urine flow. By contrast, in instances of no endogenous

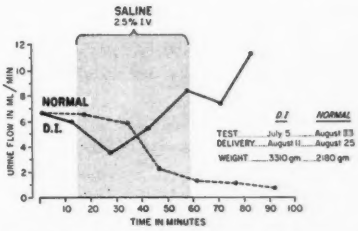

Fig. 2. Effect of hypertonic saline on urine flow in normal and diabetes insipidus pregnant patients. During pregnancy with the fetal weights estimated at 2,500 grams, there was no alteration in test responses of a normal patient and the diabetes insipidus patient as compared with those in Figure 1.

hormonal supply, that is, the patient with a disturbed neurohypophysis or diabetes insipidus, there is a sustained or increased polyuria. These changes are illustrated graphically in Figure 1.

In Figure 1 it is noted that both patients had an initial polyuria. Upon injection of the 2.5 per cent saline the polyuria increased in the insipidus patient, while in the normal subject (C.W.) the endogenous antidiuretic hormone caused a sharp drop in the diuresis. When supplied with exogenous hormone intravenously, the insipidus patient had a sharp fall in the polyuria, thus revealing a deficiency in the hormone per se and not an ineffective end organ, the renal tubule. Upon oral rehydration of the normal subject, the polyuria resumed and when given exogenous antidiuretic hormone intravenously, the diuresis ceased. The similarity between the

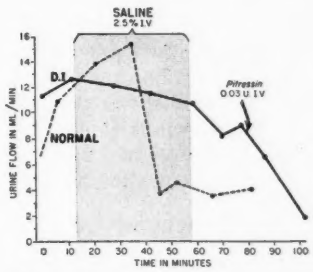

Fig. 3. Effect of hypertonic saline on urine flow in postpartum diabetes insipidus patient as compared with normal patients. After two normal gestation periods and deliveries the same diabetes insipidus patient showed a sustained polyuria after administration of hypertonic saline.

curves whereby endogenous and exogenous hormone brought about a cessation of the water diuresis in the normal subject is readily seen.

In Figure 2 the results of a similar study in pregnant patients are seen. This is the same diabetes insipidus patient as shown in Figure 1. The fetal weights were estimated at 2,500 grams and on the right of Figure 2 the dates of the tests, delivery dates, and the weights of the infants at birth are given. The test responses are the same with the insipidus patient showing a sustained and increasing polyuria while the normal subject had an antidiuresis. In the insipidus patient the pregnancy did not alter her response, and if transplacental transfer of hormone is a fact to be considered, it is certainly not reflected.

In Figure 3 the test response of a normal patient (B.L.) is compared with the same diabetes insipidus patient now postpartum. After the hypertonic salt, the normal subject shows a sharp antidiuresis and the insipidus patient shows a sustained polyuria, still indicative of a disturbed neurohypophysis.

PARTURITION

The gestation periods of the diabetes insipidus patient were normal during both pregnancies. Under our observation following routine induction by rupture of the membranes and an enema, she went into spontaneous labor and delivered after 8¾ hours without instruments and without posterior lobe extracts. No antidiuretic pitressin tannate in oil® was given for over 24 hours prior to the induction of labor.

The delivery of the twin pregnancy was carried out elsewhere. Following a routine induction without posterior lobe extract, the patient delivered twin boys with the labor lasting 1¾ hours. The infants weighed 2,500 and 2,800 grams. At the present time all children are normal.

DISCUSSION

From the data presented in this patient, wherein no doubt exists as to the validity of a disturbed neurohypophysis, parturition was initiated and carried through without posterior lobe excitants. The question of a transplacental oxytocin supply from the fetus cannot be answered completely, but it appears unlikely for the hypertonic saline response, testing for antidiuretic substance, was that of a true diabetes insipidus patient when the fetus weighed 2,500 grams, and through the gestation periods the severity of the diabetes insipidus was unaltered.

Of the reported cases of associated diabetes insipidus in pregnancy, parturition was normal in most instances. The diagnosis might have been inaccurate in some for no patient had a hypertonic saline test. An abnormal parturition appeared related to entities not directly associated with diabetes insipidus, as for example, Engstrand and Izquierdo's patient suffered from a toxemia of pregnancy and Lake's patient must have had a lesion of the anterior pituitary lobe. In Marañon's patient a primary dystocia may have been the factor, but the bizarre onset of the diabetes insipidus, along with concentric visual field changes, headaches, and patternless neurologic findings, suggests the presence of a functional element.

In the study the investigation of the oxytocic factor has been through an appraisal of the antidiuretic excitant, but the method appears valid for a loss of one posterior lobe activity is accompanied by a loss of the others.

SUMMARY

A facet of the hormonal relationship to parturition in the human has been examined. From this clinical investigation it appears that an intact neurohypophysis is unessential for normal gestation and parturition.

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POSTOPERATIVE PSEUDOMEMBRANOUS ENTEROCOLITIS

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PSEUDOMEMBRANOUS enterocolitis, a relatively rare surgical complication, in recent years has received an increasing degree of attention, leading to a belief that the lesion is related in some way to recently adopted methods of therapy.

For this study, clinical, laboratory, and necropsy records for the period from January 1, 1925 through December 31, 1952 were reviewed. Only cases in which the diagnosis had been confirmed at necropsy were included.

One hundred and seven cases were found in which pseudomembranous enterocolitis occurred in patients who had recently undergone surgical procedures. In 13 of these cases the lesions were localized to small segments of the bowel and were not considered as important factors in the cause of death. These cases were considered separately, leaving 94 cases in which the lesions were extensive and were thought to be primary factors in causing the death of the patient.

RESULTS

Clinical aspects. Incidence.—There has been no statistically significant increase in the incidence of postoperative cases of generalized pseudomembranous enterocolitis at the Mayo Clinic during recent years (Fig. 1). From 1925 through 1938, there were 45 cases of generalized pseudomembranous enterocolitis diagnosed at necropsy. From 1939 through 1952, there were 49 cases so diagnosed. Although in the years 1947, 1951, and 1952 there were more cases than in other years, there has likewise been a recent increase in the total number of surgical patients at the Mayo Clinic, and this slight increase is not statistically significant.

That there has been a marked increase in clinical interest in this lesion at the Mayo Clinic, however, may be seen in the fact that prior to 1948 not 1 case of pseudomembranous enterocolitis was correctly diagnosed ante mortem, while, in 14 of the 26 cases in which this lesion was observed at necropsy since 1948, a correct diagnosis had been made before death.

Surgical procedures.—In 87 of the 94 cases of extensive disease the operative procedure involved opening the peritoneal cavity. In 77 cases the gastrointestinal tract was directly involved in the surgical procedure. There was a wide variety of lesions for which these patients underwent surgical procedures (Table I), but the commonest lesion found was carcinoma of the colon (41 of 94 patients).

Since in so many of our patients pseudomembranous enterocolitis had developed after surgical procedures for carcinoma of the colon, it seemed pertinent to determine whether this fact was of real significance. We determined the total number of cases in which necropsy was performed after surgical procedures for the 4 commonest surgical diagnoses in our series. Because of the accessibility of data, the 9 year period from 1943 through 1951 was selected for study. These figures were then compared with the number of patients who had died of pseudomembranous enterocolitis following these surgical procedures. The results are given in Table II. The incidence in patients examined at necropsy following surgical procedures for carcinoma of the colon was more than twice the incidence in those following surgical procedures for peptic ulcer and still further exceeded the percentages for cholecystitis and carcinoma of the stomach. There can be no doubt, therefore, that the incidence of pseudomembranous enterocolitis is much higher after operations for carcinoma of the colon than for any other condition.

Abridgment of thesis submitted by Dr. Pettet to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Pathology.

From the Mayo Foundation (Dr. Pettet) and the Section of Pathologic Anatomy (Dr. Baggenstoss) and Sections of Medicine (Dr. Dearing) and of Surgery (Dr. Judd), Mayo Clinic.

Age and sex.—Thirty-eight of the patients were women and 69 were men. This incidence parallels the incidence of men and women seen at necropsy at the Mayo Clinic. The age of the patients varied from 9 months to 76 years, the average age being 50 years for women and 3 years for men. This age incidence is what one would expect when one considers the primary complaints for which the patients were treated. It is not thought to indicate a particular age prevalence in the occurrence of the pseudomembranous enterocolitis itself.

Preoperative condition.—In 86 cases an estimate of the preoperative condition of the patient was recorded. Thirty-four patients were considered to be in good general condition, 24 were in fair condition, and 28 were thought to be in poor condition.

Clinical course.—In 65 cases clinical data were sufficiently complete to permit careful evaluation. The impression gained from a review of these clinical histories is that in most cases the patients withstood operative procedures with little or no more difficulty than would be expected in the average patient undergoing the operation. After an apparently uneventful period varying in length from a few hours to an extreme of 39 days, with a mean of 3½ days, the patient evidenced signs or symptoms of some complication. In most cases there was a fairly abrupt change which in retrospect leads one to suspect the onset of pseudomembranous enterocolitis. From that point on, the clinical course became rapidly and progressively worse until death, which occurred in a few hours to 11 days.

Cramping abdominal pain and distention were most often the first symptoms noted, being the initial complaint recorded in 32 of the 65 patients, either alone or associated with nausea and vomiting or diarrhea. In an additional 11 cases distention occurred later, in most cases during the first 24 hours following the suspected onset of pseudomembranous enterocolitis. The distention which these patients exhibited was marked and did not subside with intubation.

Nausea and vomiting occurred as an initial symptom in 16 of the 65 cases, most frequently in association with distention and diarrhea. It was recorded as a later symptom in 17 cases.

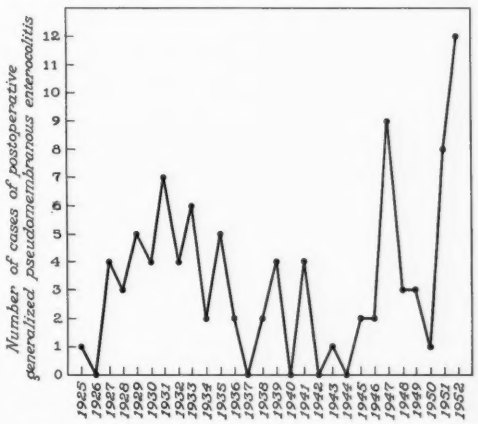

Fig. 1. Cases of postoperative generalized pseudomembranous enterocolitis at the Mayo Clinic.

It is probable that the incidence of this symptom would be higher were it not for the fact that the majority of patients were intubated shortly after onset of symptoms. In several of the cases it was noted that there seemed to be an excessive amount of fluid removed via gastric suction.

Fifteen of the 65 patients had diarrhea as an initial symptom, and in 16 cases it was recorded as a later symptom. The explosive onset of a voluminous discharge of watery green or yellow-brown stool is a very dramatic change and has come to be associated with pseudomembranous enterocolitis in the minds of many clinicians. At present, a diagnosis of pseudomembranous enterocolitis is frequently suspected at the Mayo Clinic when severe diarrhea develops following operation, and there is a tendency to believe that this symptom is present in all cases. It should be recalled, however, that less than half of the patients were noted to have diarrhea.

In 50 of the 65 cases, shock was a predominant finding during the final few days of life. (Shock was considered to be present if the systolic blood pressure fell markedly or if the patient exhibited the clinical picture of pallor, sweating, tachycardia, and so forth.) In most cases this was observed on the day of suspected onset of pseudomembranous enterocolitis, but in only 19 cases was it one of the first symptoms noted. In the remaining cases,

TABLE I.—OPERATIVE DIAGNOSES IN 107 CASES OF LOCALIZED AND GENERALIZED PSEUDOMEMBRANOUS ENTEROCOLITIS IN WHICH NECROPSY WAS PERFORMED

Diagnosis	No. of cases
Carcinoma of colon	43*
Peptic ulcer	12†
Cholecystitis	11*
Carcinoma of stomach	8†
Chronic ulcerative colitis	2
Benign prostatic hypertrophy	4†
Carcinoma of bladder	3†
Appendicitis with rupture	3†
Malfunctioning gastroenterostomy	2
Pelvic inflammatory disease	2
Exophthalmic goiter	2*
Miscellaneous	15*

*Two patients in this group had localized lesions.
†One patient in this group had localized lesions.

it followed the onset of marked distention, vomiting, or diarrhea. The time which elapsed between the onset of shock as recorded on the chart and the death of the patient varied from 2 hours to 9 days. Fifty per cent of the patients died within 12 hours, and 70 per cent died within 24 hours of the time they were first noted to be in shock. Only 6 patients lived more than 48 hours after shock was recorded.

In all but 11 of the 65 cases on which data were analyzed, there were elevations of temperature to more than 100 degrees F. at some time during the postoperative course. In 21 cases, this occurred immediately or very shortly after operation and was not thought to be related to the final episode, except that it indicated some complicating factor, which in most cases was peritonitis or pneumonia. Thirty-one patients had elevation of temperature, generally marked, during the period between the change in the clinical course and death. In the great majority of these cases the rise in temperature followed closely other evidences of complications. In many cases there was a very sharp rise terminally, with final temperatures of 105 to 107 degrees F.

In 11 cases there was clinical evidence suggesting cerebral damage. Nine patients had marked mental confusion or delirium during the last 24 hours of life. One patient had a sudden unexplained loss of consciousness without obvious cause and with no preceding indications of difficulty. One patient had a sudden onset of signs and symptoms of a cerebrovascular accident, which was the diagnosis made by the neurologist. In 5 of these cases, including the last one described, complete postmortem examination was performed, but no cerebral lesions were found which might account for the neurologic symptoms.

Oliguria developed in almost all of the patients who lived more than a few hours after the marked change in their condition. This was accompanied by evidence of marked dehydration, fluid and electrolyte imbalance, and uremia.

The length of time which elapsed between the suspected onset of pseudomembranous enterocolitis and the death of the patient varied from 3 hours to 11 days. Thirty of the 65 patients (46 per cent) died within 48 hours, while 53 (81 per cent) died within 4 days.

In reviewing the pathologic material, it was found that in 13 cases the pseudomembranous lesions of the intestine were so limited in extent that it would be difficult to maintain that they played any significant part in the death of the patient. These cases, therefore, were considered separately. A review of the clinical material in these cases supports this segregation. In no instance does the history suggest a sudden change in the course of the patient which might lead one to suspect the onset of an intestinal lesion. The operative diagnoses are indicated in Table I.

Chemotherapeutic and antibiotic drugs.—Since 1939, there have been 40 cases of fatal postoperative pseudomembranous enterocolitis diagnosed at necropsy in which one or more of the chemotherapeutic or antibiotic drugs had been administered. In 18 of these cases either aureomycin or terramycin had been given, usually in combination with penicillin or streptomycin. In 31 cases penicillin

TABLE II.—NECROPSIES FOLLOWING VARIOUS SURGICAL PROCEDURES, 1943 THROUGH 1951

Surgical diagnosis	No. of necropsies	Cases with pseudomembranous enterocolitis	
		No.	Per cent
Carcinoma of colon	203	21	10.3
Peptic ulcer	84	4	4.8
Cholecystitis	44	1	2.3
Carcinoma of stomach	114	1	0.9

ha been given, while in 23 cases streptomycin ha been given.

aboratory findings.—In recent years, as aw reness of the possibility of pseudomembr ous enterocolitis as a postoperative compl tion has increased, laboratory investigati of these patients has been more complete th was formerly the case. In a majority of th patients hemoconcentration, azotemia, m bolic acidosis, hypochloremia, and hypop ssemia have been found to develop. Other fi gs have been leucocytosis with increase in utrophils, and increased erythrocyte sedim tation rate. Roentgenograms of the abd n have shown generalized intestinal dist n. In 9 cases fecal material from the pati was cultured before death. Eight were re ted as negative for pathogens. In 1 case M coccus pyogenes was the only organism wh grew on culture.

ur patients had evidence of azotemia of m rate degree before operation was perfo ed. Two of these patients had benign pr atic hypertrophy with pyelonephritis, 1 ha ystoureteropyelonephritis, and the fourth ha obstructing duodenal ulcer with severe vo ting. There is nothing to indicate that th patients had the lesions of pseudomembr ous enterocolitis before operation, and the ur mia was not of a degree to make it likely that the intestinal lesions were uremic in origin. There have been reports, however, of similar lesions of the gastrointestinal tract in patients who have died in uremia.

Bacteriologic aspects. Previous to 1952, ante mortem stool cultures had been performed in very few cases of pseudomembranous enterocolitis. Those that were done were almost uniformly reported as negative for enteric pathogens. Postmortem stool cultures were similarly negative for pathologic bacteria and fungi.

Because of the recent interest in the effects of terramycin and aureomycin on the flora of the bowel, stool examinations during the latter part of 1952 have included culture for Micrococcus pyogenes. In this period, 5 patients dying with generalized pseudomembranous enterocolitis have been found to have Micrococcus pyogenes organisms in large numbers in cultures of their feces taken at necropsy, with a marked depression or complete absence

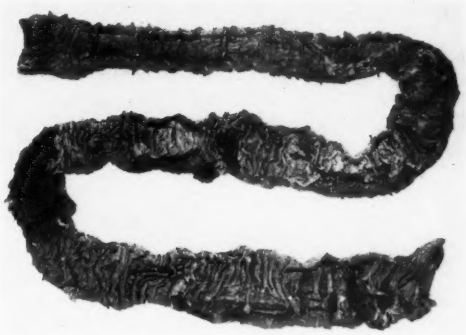

Fig. 2. Gross appearance of pseudomembrane covering a large segment of ileum. Scattered large and small plaques can be seen.

of the flora usually present in the intestinal tract. All of these patients had received terramycin. In 3 cases, studies of the sensitivity of these organisms to the various antibacterial drugs revealed a high resistance to terramycin, aureomycin, and streptomycin particularly. The drug to which they were found to be uniformly sensitive was erythromycin. Three of these cases are discussed by Dearing and Heilman and are included in their report as Cases 39, 40, and 41. In the remaining 2 cases, postmortem stool and blood cultures revealed Micrococcus pyogenes in significant numbers, but sensitivity studies were not done. Both of these patients had received terramycin.

Since most of the stools previous to this have been cultured on media which are not suitable for the demonstration of Micrococcus pyogenes, it is impossible to determine how

TABLE III.—PSEUDOMEMBRANOUS ENTEROCOLITIS; LOCATION OF LESIONS (107 CASES)

Site	No. of cases
Extensive	
Small intestine	44
Small and large intestine	24
Large intestine	12
Duodenum and small intestine	5
Esophagus, small and large intestine	2
Stomach and small intestine	2
Duodenum, small and large intestine	2
Esophagus, stomach, and small intestine	2
Stomach, duodenum, and small intestine	1
Localized	
Jejunum	3
Ileum	4
Cecum	4
Ascending colon	2

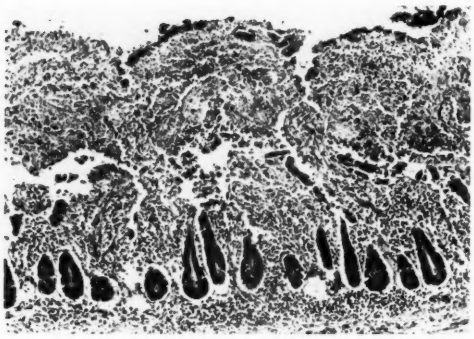

Fig. 3. A pseudomembrane, composed of necrotic cellular debris, fibrin, and inflammatory cells, covers the mucosal surface. Bacterial colonies can be seen on the luminal side of the pseudomembrane. Inflammatory cells infiltrate the entire mucosa. The superficial cells of the mucosal glands are completely necrotic, while the basal cells are still viable. Hematoxylin and eosin, ×70.

many of the patients in the past may have had this organism in their stools in excessive numbers.

Pathologic aspects. Gross appearance.—The intestinal tract was markedly dilated in the majority of cases, either in part or throughout its entire length. In 59 (63 per cent) of the 94 cases of generalized pseudomembranous enterocolitis, there was evidence of peritonitis. In 24 cases an obvious etiologic factor for the peritonitis was found at necropsy. In the remaining 35 cases no definite etiologic factor was found.

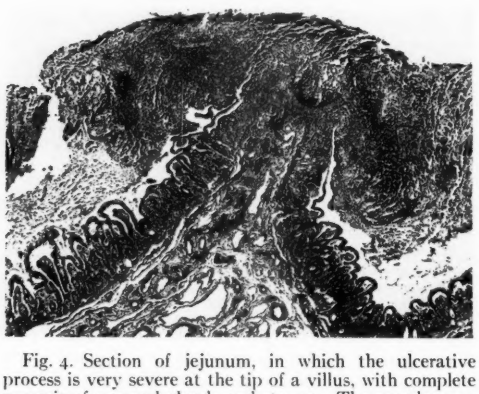

Fig. 4. Section of jejunum, in which the ulcerative process is very severe at the tip of a villus, with complete necrosis of mucosal glands and stroma. The pseudomembrane is attached at this point. The epithilium of the crypts is less severely involved. Hematoxylin and eosin, ×21.

When the intestine was opened, large quantities of gas, and liquid feces escaped from the lumen, and as much as 5,000 cubic centimeters of liquid feces were measured. Careful examination of this liquid often revealed fragments of yellow-tan or greenish tissue which varied in size from small flecks to large fragments. The mucosal surface of the bowel was characteristically covered with the yellow-green or tan friable pseudomembrane which gives this lesion its name (Fig. 2). This membrane varied in extent from small scattered plaques of varying size to a diffuse process extending for a distance of several feet. In most cases this pseudomembrane separated easily from the underlying mucosa, which varied from a diffusely injected surface to a fairly normal appearance. In many cases, if the membrane had not been seen, the bowel might not have been considered grossly remarkable.

It is entirely possible that this easily separated pseudomembrane might be missed if the bowel were washed with a strong stream of water prior to examination, as is the practice in many laboratories.

Location and extent of lesions.—In 94 cases pseudomembranous lesions were widespread throughout the bowel (Table III) and at necropsy were thought to be the primary cause of death. In 13 cases the pseudomembranous inflammation was localized to a segment of bowel of about 20 centimeters or less. It was not believed that so localized a process could be considered the cause of death, and, therefore, these cases were considered separately.

Histologic appearance.—The outstanding histologic finding was the presence of a pseudomembrane composed of necrotic cellular debris, fibrin, a variable number of inflammatory cells, and occasionally mucus (Fig. 3). This pseudomembrane usually covered the ulcerated mucosal surface. Bacterial colonies were frequently seen on the luminal side of the pseudomembrane and were occasionally seen in the walls of the mucosal glands.

Occasional sections revealed a fairly intact mucosa covered by a layer of fibrin and inflammatory cells. It is probable that these represented the earliest stage of development, but sections showing this change were rare, probably because of the ease with which such a

ucosal exudate can be washed or rubbed off e surface of the bowel.

Although the entire mucosa was often rotic, examination of all stages of the proc- indicated that the superficial portion was olved first (Fig. 3).

In the jejunum and ileum the process was n most severe in, or limited to, the tips he villi, and the membrane was seen to be ached to the points of most extensive mal involvement at the tips of the villi . 4).

some cases the mucosa was infiltrated by oderate number of inflammatory cells. cells were predominantly neutrophilic morphonuclear leucocytes, with varying bers of plasma cells and lymphocytes. sionally, the cellular infiltration extended the submucosa and muscularis.

ucosal and submucosal vessels were widely ated in most sections, and hemorrhage was sometimes marked (Fig. 5). This was ass ed to result from diapedesis of erythroes, since there was rarely any evidence of mage to the vessel walls. Occasionally, mu sal vessels were occluded by hyaline thr mbi.

most cases submucosal edema was extreme, and in many cases there was an exudation of fibrin, so that the edematous submucosa was filled with a fibrinous network. The edema frequently involved the muscularis propria and Auerbach's plexuses.

Many histologic sections revealed various stages of the necrotic process in close approximation, so that small areas in which the entire mucosa was completely necrotic bordered on areas in which the mucosal glands showed only early necrosis of the superficial cells or moderate hyperproduction of mucus.

The gross and histologic material from the patients who were found to have resistant Micrococcus pyogenes organisms in their stools was reviewed carefully and compared with the material from lesions found in the remaining cases. Although at the time of necropsy the pseudomembrane seemed less adherent and somewhat more mucoid in these cases, the formalin-fixed tissue revealed no marked differences, and histologic changes were similar to those described previously.

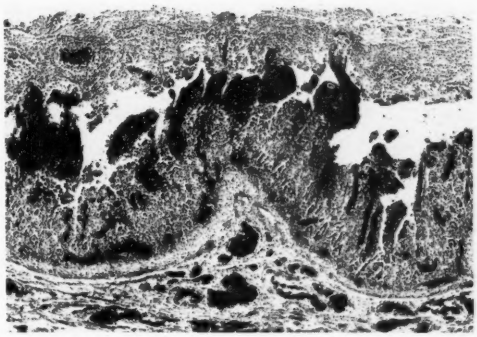

Fig. 5. Severe hemorrhage in the mucosa and marked dilatation of submucosal vessels are seen in this section. Hematoxylin and eosin, ×29.

The histologic changes in the 13 cases of localized pseudomembranous lesions were similar to those found in the more extensive form of the disease.

COMMENT

Although pseudomembranous enterocolitis is a relatively rare postoperative complication, in the past 28 years 94 patients at the Mayo Clinic have died during the postoperative period with this intestinal lesion as the major pathologic finding at necropsy. It is thus important for clinicians and pathologists to be aware of the possibility of its occurrence and to study it intensively when it does occur. Such investigation may lead to that factor or combination of factors which produces the pathologic changes.

There have been two suggestions of possible etiologic factors in the production of this lesion. The first is that of Penner and Bernheim, who believed that shock was the one common condition present in all their cases, and the second is that of Reiner and associates who suggested that aureomycin and chloramphenicol are responsible for the production of the lesion.

Our findings do not support either of these theories. Although most, if not all, of the patients in our study were in obvious clinical shock at some time prior to their death, shock was by no means always the earliest sign of a serious complication, and it usually followed other signs of gastrointestinal complications.

The lesion which is found at necropsy is an extensive denudation of the mucosa of the bowel, with tremendous quantities of fluid having been exuded into the lumen of the bowel. It is not at all surprising that in patients with such a lesion profound circulatory collapse should have developed, and it seems impossible to determine from a pathologic standpoint which occurred first.

In our cases, no one drug or drug combination was used with sufficient frequency to indicate a direct causal relationship.

That there may have been an upset in the normal balance of intestinal flora in some of the more recent cases at least is suggested by the fact that in 5 cases culture of the feces made at necropsy revealed large numbers of Micrococcus pyogenes organisms and a marked decrease or absence of the usual intestinal flora.

That an infectious agent may be important in the production of this lesion is suggested by the fact that in 71 of our cases some type of septic process was found at necropsy.

The importance of carcinoma of the colon with obstruction is suggested by the fact that in 41 (44 per cent) of our 94 cases of extensive lesions, surgical procedures were performed because of carcinoma of the colon. Twenty-six of these patients had had some degree of preoperative obstruction that had been noted by the proctologist, radiologist, or surgeon. In all of these cases the pseudomembranous lesions were found proximal to the site of the operative procedure. This finding and the fact that in most of the cases there was marked dilatation of the intestine, with general peritonitis at necropsy, suggest that intestinal obstruction, either organic or adynamic, may be a factor in producing this lesion. It is possible that the normal balance of intestinal flora may be upset in some cases by intestinal obstruction, in other cases by therapy, and in some cases by factors as yet not understood.

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TREATMENT OF PATELLAR FRACTURES

Review of 68 Consecutive Surgical Cases

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THE voluminous literature on patellar fractures is indicative of the great amount of thought given to this subject. Fractures of the patella occur t ce as often in males as in females, and the l e majority occur during the most productive decades; therefore, their management is a important economic problem. Many methods of treatment have been advocated but the results are considerably less than perfect.

Open reduction with suture of fragments, excision of all but the largest fragment, and patellectomy are the commonly employed procedures. We have used all of these in our series; however, on retrospect the indications for each have not always been well defined. Each case has been studied as to the type of fracture as well as the method of surgery employed. It was hoped that indications and contraindications might be established through a study of the good results as well as the bad.

Sixty-eight consecutive cases of fractured patella with displacement which had been treated surgically were reviewed. Twenty-three fractures had been sutured, 27 treated by excision of small fragments allowing the largest piece of the patella to remain, and in 18 instances patellectomy had been performed.

Fourteen of the patients in the series had a pre-existing disability or major concomitant injury of the involved extremity. This group represented 20.6 per cent of the entire series and the results were usually poor. Age, sex, and the time elapsed before surgery were found to be of no significance in the end results, but all cases were treated within 8 days after the injury. Only 6 of the fractures were compound and all of these were treated primarily within 8 hours after the accident. The results were not appreciably different from the simple fractures.

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OPEN REDUCTION AND SUTURE OF FRAGMENTS

Technique. The classic method of treatment is open reduction and suture of fragments. In our series heavy chromic catgut suture material was used either through parallel vertical drill holes or circumferentially and sometimes in both ways in order to establish the firmest possible fixation with the most accurate reduction. Wire suture and screws were not used.

Chromic catgut has maintained its integrity long enough to permit healing of bone to bone or tendon to bone in all but 1 of 50 patients.

Following suture of fragments the knee was immobilized in a plaster cylinder for a period of 4 weeks during which time quadriceps setting exercises were performed. After removal of the plaster, intensive rehabilitation was encouraged; however, 6 to 8 additional weeks were usually required before some semblance of normal activity could be resumed.

Results. Nineteen of the 23 cases in which suture had been performed were available for study. The results in 5 cases were considered excellent. All had been cases of transverse fractures through the waist of the patella with no discernible disability. The results in 5 others were classified as good. Some weather change pain, pain on prolonged activity, and limitation of the last 10 or 20 degrees of flexion were present. One of these cases had been an instance of a transverse fracture of the waist; the other 4 were fractures of the lower pole. Roentgenograms in these cases showed varying degrees of osteoporosis, bony proliferation, and osteoarthritis. Clinically there was grating. The results in 2 patients were considered fair. They had some pain each day and motion was limited to 75 degrees. Both walked with limps and negotiated stairs with some difficulty (Table I). Seven patients with prior disability or concomitant injury were unable to walk without support (Table II).

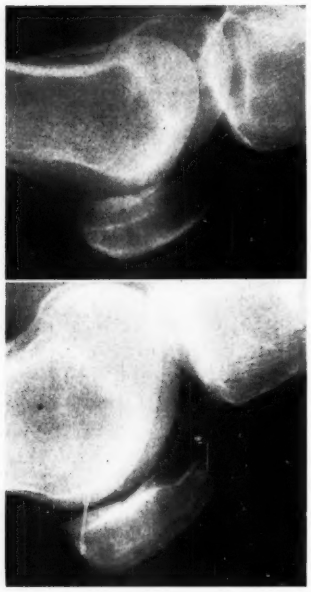

Fig. 1. Lateral views in 2 cases 4 and 7 years after suture of transverse fractures. Anatomic results are not quite perfect, but clinical results are excellent.

No patient was disabled less than 8.7 weeks and, excluding the group with concomitant disability, the average length of disability was 12.5 weeks (Table III).

The follow-up period was 2 to 15 years with an average of 6.5 years.

Discussion. The principal appeal in suturing fragments is that it may achieve anatomic restoration, but this was true in only 4 of our cases (Fig. 1).

All of these were transverse fractures through the midportion of the patella, and in each case the result was perfect. This is the type of fracture in which accurate reduction is most easily achieved and maintained. Near the poles the area of coaptation is much less than at the middle. Reduction is relatively simple, but fixation and maintenance of position are not so often successful at this site as at the waist where there is adequate coaptation (Fig. 2). The diminished area of coaptation at the lower pole allows less opportunity for healing while the amount of stress placed on fractures at either site is always the same. By this token an oblique fracture through the waist should unite easily by virtue of increased area of coaptation. This rarely occurred, however, because it was difficult to obtain accurate reduction and maintain the position of an oblique fracture by suturing since the fragments tend to slip because of the obliquity (Fig. 3).

Oblique and comminuted fractures, and fractures near the poles seem doomed to some degree of malunion because even when reduction is achieved, fixation is rarely possible by suturing. Fixation by means of screws might be more applicable to oblique fractures if anatomic reduction could be achieved. It is rarely possible to have a normal knee in the presence of malunion of the patella (Fig. 4).

Even under ideal conditions there is an important disadvantage to treatment of the fractured patella by means of suturing. Immobilization is necessary for 4 weeks during which time rehabilitation is limited. Following the immobilization period 6 to 8 weeks are required for return of function. The long period of inactivity promotes osteoporosis and soft tissue attrition. This condition is particu-

TABLE I. — END RESULTS IN UNCOMPLICATED CASES

Results	Suture of fragments		Excision of all but 1 fragment		Patellectomy	
	No.	Per cent	No.	Per cent	No.	Per cent
Excellent	5	41.7	6	35.2	10	83.3
Good	5	41.7	5	29.3	2	16.7
Fair	2	16.6	4	23.5	0	0.0
Poor	0	0.0	2	11.8	0	0.0
Total	12	100.0	17	100.0	12	100.0

TABLE II. — END RESULTS IN CASES COMPLICATED BY CONCOMITANT DISABILITY OF INVOLVED LIMB

	Suture of fragments		Excision of all but 1 fragment		Patellectomy	
	No.	Per cent	No.	Per cent	No.	Per cent
Excellent	0	0.0	0	0.0	1	25.0
Good	0	0.0	0	0.0	0	0.0
Fair	0	0.0	0	0.0	2	50.0
Poor	7	100.0	4	100.0	1	25.0
Total	7	100.0	4	100.0	4	100.0

TABLE III. — PERIOD OF DISABILITY IN PATELLAR FRACTURES (EXCLUDING THOSE WITH CONCOMITANT DISABILITIES)

Method of treatment	Shortest, wks.	Longest, wks.	Average, wks.
Suture of fragments	8.7	14.0	12.5
Excision of all but the largest fragment	6.3	16.0	12.6
Patellectomy	2.7	6.4	5.3

This table patients' disability was said to be terminated when they were (a) ambulatory without support, (b) had a range of motion from full to at least 90 degrees, and (c) had a negligible amount of pain. This table is not related to the end result study.

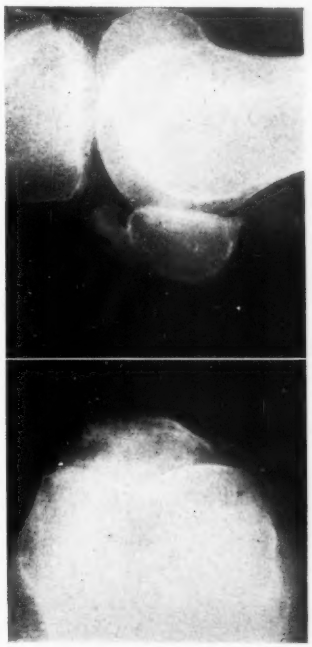

Fig. 2. Incomplete healing 5 years after suture of lower pole. Note normal relationship to condyles. Despite sclerosis and cystic changes, result is excellent.

last undesirable in cases in which there is a preexisting disability of the involved extremity.

EXCISION OF ALL BUT THE LARGEST FRAGMENT

Technique. In 1935, Thomson (12) gave impetus to the method of excising all but the largest fragment of a fractured patella. In 1939 (13) by questionnaire, he reviewed over 500 cases treated in this manner. The average disability for this group of patients was said to be 6 weeks, and only 5 per cent were reported to have any residual disability. The patients were operated upon by many different surgeons and many different methods of suture must have been used, but the results indicated that the principle rather than the technique was the important factor.

In our series the method of suture described by Thomson was originally employed, and chromic catgut was the suture material used (Fig. 5a and b). This operation consists of suturing the cut proximal end of the patellar tendon so it will lie in direct contact with the raw bone of the proximal patellar fragment. The suture is placed in the tendon and each end is threaded through parallel vertical drill holes in the remaining patellar fragment. The two ends are then tied at the superior margin of the patella. This method has the advantage of restoring the normal line of pull exerted by the quadriceps through the patella and its tendon acting upon the tibia. Smillie has stated that this method of suture permits the patella to ride higher on the femur than is normal which is undesirable. Stern and Prince (11) varied their techniques so as to bring more of the tendon into contact with the bone of the patellar fragment and hence improve the chances of healing (Fig. 6a, b). However, in so doing, the drill holes were placed in such a way as to bring the posterior surface of the tendon into contact with the patella which tends to alter the line of force by angulating the patella because it is anchored to the posterior surface of the patellar tendon both inferiorly and anteriorly. Recently Garber has varied this technique by adding an additional set of drill holes so angulated as to bring the posterior margin of the patellar tendon into contact with the posterior margin of the raw surface of the patella and to pull the tendon tightly so the remainder of its cut end is brought into approximation with bleeding bone (Fig. 7a, b, c). His early results have been excellent.

We wish to present a method of suture of patellar tendon to remaining patellar fragment which we believe has all the advantages mentioned but none of the disadvantages.

Fig. 3.

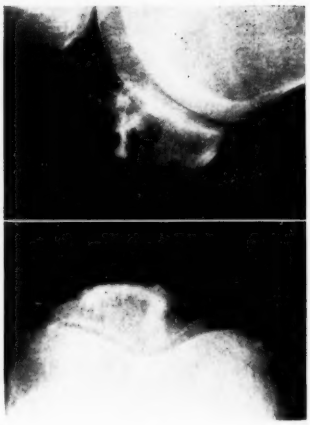

Fig. 4.

Fig. 3. Oblique fracture and follow-up views 5 years after suture. Slipping of fragments with malunion. Fair clinical result.

Fig. 4. Malunion with osteoarthritis and increasing disability 4 years after suture of the lower pole.

After careful excision of all of the small fragments by means of a scalpel, the remaining large fragment of the patella is grasped in a bone clamp and its raw edge smoothed with a raspatory, particular attention being given to the posterior margin. It is well to place a moist sponge beneath the patella to prevent any bone crumbs from dropping into the joint. By means of a small mastoid gouge it is possible then to dig a furrow in the cancellous portion of the fracture surface of the patella. This furrow is about 2.5 centimeters in breadth and 0.7 centimeter in thickness. If it is made about 1.5 centimeters deep it will adequately accommodate the patellar tendon. Three drill holes are made from the floor of the furrow proximally. Two mattress sutures of heavy chromic catgut are placed in the tendon and threaded through these holes. The bights nearest the midline share the central drill hole and the sutures are then pulled tightly to fit the tendon snugly into the furrow (Fig. 8a, b). The reflections of the quadriceps retinaculum must be carefully repaired.

This technique allows the patella to be pulled downward, the extensor mechanism to be shortened, greater apposition of tendon to bone as well as the double suture strength suggested by Garber. In addition, it insures the normal line of pull through the patella. This method has been employed in 4 cases with excellent early results, the most recent case 6 months ago, and the earliest 2 years ago.

Results. Twenty-one of 27 patients who were treated by excision of all but the largest fragment were available for follow-up study. In 6 instances the results were considered excellent although regeneration of the lower pole was present (Fig. 9). The results in 5 patients were good. These patients showed regeneration of the excised fragments and some had osteoporosis and early osteoarthritic

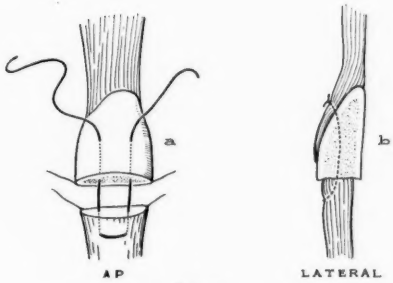

Fig. 5.

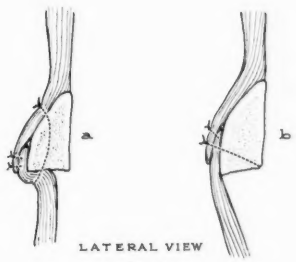

Fig. 6.

Fig. 5. Anteroposterior and lateral views of Thomson's method. Redrawn from Smillie (11).

Fig. 6. Lateral views of, a, Stern's and, b, Prince's method. Redrawn from Smillie (11).

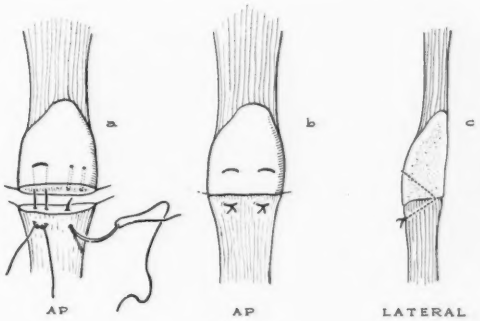

Fig. 7.

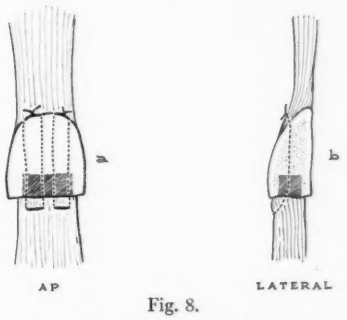

Fig. 8.

Fig. 7. Garber's technique. a and b, Anteroposterior; c, lateral view. Redrawn from Garber (7).

Fig. 8. Author's technique. a, Anteroposterior view of new method of suture; b, lateral view.

changes. There was usually slight limitation of flexion and pain upon increased activity. The results in 4 cases were fair. In 2 of these the presence of tilting and regeneration of resected fragments was noted. Two other patients had increasing pain and decreasing motion with tilting and osteoporosis following excision of the upper pole (Fig. 10). Only 3 of 68 fractures were confined to the upper pole. In 6 cases the results were poor. One of these involved the upper pole and regeneration, tilting, and osteoarthritis were present only 26 months after injury. In another case osteoarthritis, regeneration, and tilting were demonstrated (Fig. 11a, b and Table I). Four of the poor results occurred in patients who had pre-existing disability of the injured limb (Table II). Some patients returned to reasonable activity in 7 weeks, but excluding the poor results in which instance the patients never regained reasonable activity, the average duration of disability was 12.6 weeks (Table III). The follow-up period for this group was from 2 to 9 years with an average of 4⅔ years.

In many patients treated by excision of all but the largest fragment the results seemed to be good at early follow-up examination, but in those followed for longer periods the results were not so good at later follow-up. Several patients volunteered the information that they believed after 2 or 3 years that they began to lose some function and to have more pain. Actual measurements of motion over a long period of time were available on only 5 patients and each had some loss of motion, as much as 50 degrees in 1 case.

Discussion. The presence of small spicules of bone plus close apposition of tendon to bleeding bone promotes regeneration which is

Fig. 9.

Fig. 10.

Fig. 9. Patellofemoral and lateral views 5 years after excision of lower pole. Note proliferation of pole as well as aberrant ossification but articular surfaces are smooth and result is excellent.

Fig. 10. Lateral view 2½ years following excision of upper pole. Notice abnormal tilting and proliferation as well as loose fragments. Poor clinical result.

in reality a histogenesis of tendon to bone. A certain amount of new bone formation in the patellar tendon is permissible and does not hinder function. However, in 2 cases, one an upper pole excision and the other a lower pole excision, there was a great proliferation of bone extending into the tendon and the extensor retinaculum. In these cases the results were poor. Tendon to bone suture may heal more quickly than bone to bone, but if the early activity that is permitted tends to cause bony proliferation, the gain in time may be more than lost by a decrease in ultimate function. Regeneration of bone was far more prominent in cases of excision of fragments than in patellectomies, probably because of the approximation of tendon to bone.

The fragment retained is for the purpose of maintaining a fulcrum in the extensor mechanism of the knee. Whether or not a fulcrum is essential for good knee function is a widely debated subject with much clinical evidence to show that a patellectomized knee can function as well as its normal partner. The normal patella while serving as a fulcrum makes use of 7 articular facets as it moves smoothly over the femoral condyles. The inferior pole of the patella contacts the femur only in hyperextension and hence might be dispensable. However, if more than the lower pole is removed normal patellofemoral rhythm is disrupted (Fig. 12). O'Donoghue pointed out that the patella loses its stability when more than one-third of it is removed. Many of our patients showed unstable or rocking patellas clinically even when two-thirds of the patella was intact.

Lateral roentgenograms often showed tilting of the patella in relation to the condyles of the femur. This caused the rough edge of the patella to be dragged over the condyles. Tilting also disrupts normal articulation of the patellar facets with the femoral condyles (Fig. 13). We believe that this is the cause of the osteoarthritis which occurs more frequently in this group than in others (Fig. 14).

The tilting is due to the manner of fixation of tendon to remaining patella. Thomson,

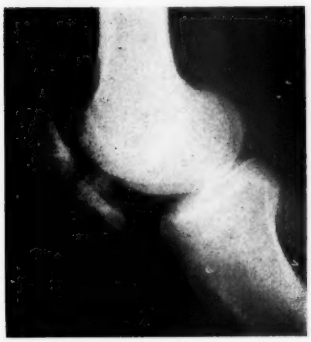

Fig. 11.

Fig. 11. Marked proliferation and ossification of patellar tendon 3 years after excision of lower pole. Poor clinical result.

Fig. 12. Normal knee in flexion, extension, and midposition. Lower pole does not contact femur. Note normal angulation of patella in extension and midposition.

Fig. 12.

Stevens, Prince, and Garber have advocated different methods of suture; it seems that the position of the drill holes controls the anteroposterior tilt of the remaining portion of the patella.

We believe that if good long term results are to be obtained by allowing a single fragment to remain, that fragment should be the proximal two-thirds or more of the patella. Particular attention must be paid to the technique of suture because if the position of function of the patella is altered, the result will ultimately be poor.

In all cases there was some regeneration of the lower pole after it had been excised, but this area has little contact with the condyles and it does not seem a direct cause of osteoarthritis. Trauma at the time of injury has been implicated as a cause of late osteoarthritic changes, but in over 100 cases of patellectomy reported by several authors mention of osteoarthritic change is made only once. In many of these cases in which the patella had been markedly comminuted, the trauma must have been severe.

PATELLECTOMY

Technique. One of the most important operative details in patellectomy is hyperextension of the knee. This is accomplished by placing the heel on a sandbag. A transverse incision, slightly concave upward, permits careful excision of all bony fragments, many of which are discovered only by palpation. Two rows of mattress sutures are placed in proximal and distal tendons and retinacula, and after all sutures are in place they are tied

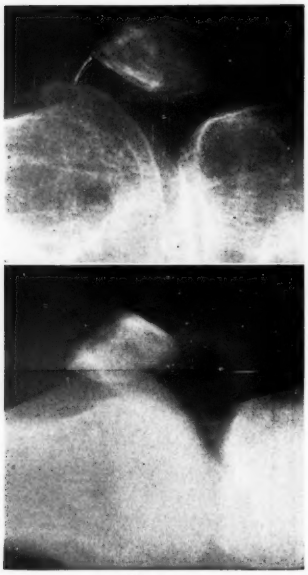

Fig. 13.

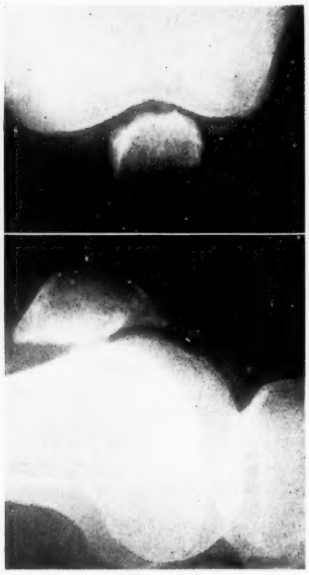

Fig. 14.

Fig. 13. Lateral views of remaining fragment of patella, below, immediately following surgery, above, 6 years later. Note abnormal tilting, loose fragment, and severe osteoporosis. A poor clinical result.

Fig. 14. Lateral and patellofemoral views 3 years following excision of the lower pole. Note proliferation of pole, abnormal tilting, and articular roughening. Good result which was considered to be excellent 1 year after operation. Motion is diminishing and pain is increasing.

firmly so as to imbricate the tissues and shorten the extensor mechanism. A posterior splint in hyperextension is used for 2 weeks during which time quadriceps setting is taught. Following removal of the splint, active knee motion is encouraged. Some of the patients progress rapidly while others are fearful. The latter are encouraged but never forced.

Results. In our series it was possible to study 16 of 18 patients treated by excision of the patella. Eleven had excellent and 2 good results (Table I). One of the latter complained of occasional stiffness and some pain after a round of golf, but no clinical weakness or limitation of motion could be found though bony proliferation was marked (Fig. 15). Results in 2 cases were fair and in 1 case poor. These patients all had pre-existing disability or severe concomitant injury in the involved extremity. One of the patients with a result considered excellent suffered a compound Pott's fracture at the time of patellar fracture (Table II). The others all had reasonably good function 3 to 6 weeks after operation, though many continued to improve for a period of as long as 6 months. The follow-up study was from 6 months to 7½ years. The average period of disability, excluding concomitant injury, was 5.3 weeks (Table III).

Discussion. Patellectomy had generally been reserved as a heroic procedure in the treatment of patellar fractures. However, in 1937 Brooke (1) advocated total excision of the patella for all fractures. He reported on a small series of cases following which the injured joint was equally as good as the normal opposite knee. These cases were corroborated by Hey-Groves, who took the view that the excellent function of patellectomized knees was the result of shortening the extensor mechanism. Ten years later Brooke (2) reported on a series of 37 cases with a follow-up

Fig. 15.

Fig. 16.

Fig. 15. Marked ossification of soft tissues without arthritic changes 5 years after patellectomy. Degree of proliferation has not changed since 6 months after operation.

Fig. 16. a, Osteoporosis present 3 months postoperatively. b, Almost disappeared after 6 months.

period of 5 to 15 years. The results in all cases were either good or excellent. Some patients had returned to reasonable activity within 3 weeks and practically all within 6 weeks after injury. This has been true in our series. In 1942 Sten Friberg reported on 32 patellectomies for various indications. The results were good or excellent in 85 per cent of these cases. He described a tendency to regeneration of bone in place of the excised patella and observed that while this was not detrimental to the end result, more regeneration was exhibited in the patients with poorer results. The regeneration of excised portions of patella was noted experimentally in dogs by Carey, Zeit, and McGrath, who found that the amount of regeneration was proportional to the amount of early activity allowed after total excision of the patella.

The first significant series of such cases in this country was reported by Dobbie and Ryerson in 1942. They described 16 cases, all with excellent results. The follow-up period was from 2 to 41 months. Horwitz and Lambert reported 19 cases with short follow-up studies and concluded that all patients had achieved optimum results within 6 months after surgery (In none of our cases was there any appreciable change after the first 6 postoperative months.) (Fig. 16). They emphasized Hey-Groves' opinion that shortening of the extensor mechanism was important to obtain good results and advocated that 1.6 centimeters was the optimum amount of shortening. Schmier mentioned regeneration in the body of the patellar ligament and believed that it gave thickness to the structure and might serve as a substitute fulcrum to hold the extensor mechanism anteriorward, and also that it might contribute to the excellent function often seen following patellectomy. We have often seen hypertrophy and thickening of the tendon without ossification. In addition to serving as a fulcrum the hypertrophied tendon may afford some protection to the condyles.

Smillie described late degenerative changes following patellectomy in a knee that had not

functioned well. Bruce and Walmsley describe osteoarthritic changes which occurred in patellectomized rabbits. We have not seen osteoarthritis in our series except in those patients who had poor results due to disability. Inability to extend the patella completely has been described by Smillie and has been seen by us in 1 case not included in this series. This condition was corrected surgically by shortening the extensor mechanism. It would seem safer to err on the side of too much shortening rather than too little, because it is possible to stretch the extensor mechanism, but if it should be too lax it can only be corrected surgically. Inability to attain the last few degrees of extension is most disabling because such a knee cannot be locked in extension and, therefore, is unstable. In our experience it is not often possible to shorten the extensor mechanism more than 2 centimeters which we prefer rather than risk having it too long.

The principal objections to patellectomy are the appearance of the knee and the loss of protection to the femoral condyles. The necessity of a patella for normal function seems disproved on a clinical basis even despite much experimental evidence proclaiming its essential nature. The unusual contour of the knee may be disturbing to some patients, particularly young women. Protection of the femoral condyles is perhaps more theoretical than real, because in kneeling the weight is borne on the tibial tubercle and not on the patella.

Rehabilitation is handicapped in all cases of patellar fractures because it is never possible to instruct the patients in quadriceps exercises before surgery as is done in other knee surgery, and it is often difficult to initiate quadriceps activity postoperatively. The patients are disposed to use hip flexors, glutei, and dorsiflexors of the ankle rather than the quadriceps. The very early return to function with diminished period of disability following patellectomy is perhaps its greatest advantage. Another important advantage of patellectomy is the diminished incidence of undesirable late symptoms, such as improper angulation and function of the patella with subsequent osteoarthritis and disability.

SUMMARY

It was assumed that a close study of the end results of a series of fractured patellas treated in three different ways might yield some information as to the suitability of each method for treatment of different types of fracture. Many impressions have been gained and have been supplemented by the existing literature.

Best results in suturing patellar fragments may be anticipated when the fracture is near the middle, is not comminuted, and is transverse rather than oblique.

Fractures involving the distal one-third or less of the patella may be treated by excision of all but the largest fragment. The manner of suture is of importance. We have proposed a technique which combines the advantages of other methods.

Patellectomy is the treatment of choice in both comminuted fractures and rare fractures of the upper pole. The results obtained in our series and by others and the lessened period of disability following patellectomy suggest that this procedure is applicable to all patellar fractures with displaced fragments.

CONCLUSIONS

1. Good results may be anticipated following open reduction and suture if there are only two fragments and the fracture is transversely situated near the waist. Open reduction and suture are contraindicated in other cases.

2. Good results may be anticipated following excision of all but the largest fragment if that fragment is the upper two-thirds of the patella and if the technique of suture is such that it will allow the patella to remain in normal relation to the line of quadriceps pull and the femoral condyles. Otherwise it is contraindicated.

3. Patellectomy is definitely indicated in comminuted fractures involving a major portion of the patella and in those rare fractures involving only the upper pole. It is rarely contraindicated.

4. Good results cannot be assured by any method if there is a pre-existing disability or severe concomitant injury but patellectomy does offer the best opportunity for a good result.

5. The period of disability is approximately half as long following patellectomy as after other methods of treatment.

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SURGICAL MANAGEMENT OF MANDIBLE INVADED BY ORAL CANCER

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CANCER within the oral cavity often arises from or extends on to the mucosa of the mandible. This integument is but a few millimeters in thickness and in every case the possibility of bone involvement must be considered to determine the proper extent of surgical removal. In addition to this direct invasion of the alveolar cortex by the primary growth the mandible may become involved in the malignant disease by spread through the mental foramen or from adjacent lymph nodes which have been destroyed by metastatic cancer (Fig. 2). A properly planned surgical approach includes the removal of a necessary amount of mandibular bone but should not be needlessly destructive. A consideration of certain anatomic factors aids in the formation of a rational scheme which is applicable to the individual case rather than one in which treatment is based on routine.

Bone is considered to be invaded when the cancer is fixed to it or is of such extent that it must have penetrated the thickness of the skimpy covering of the alveolus. Bone is a barrier to cancer because of its density. Superficial growths must be presumed to have involved periosteum before penetrating more deeply. This assumption is not disclosed by x-ray examination. Technical difficulties prevent the preparation of delicately revealing x-ray pictures of the mandible. Dental films permit more accurate visualization of those areas suitable for this technique. When more advanced erosion is shown, valuable information may be gained from x-ray studies. The penetration is greater than revealed since rather gross changes are preceded by less obvious ones.

Having decided to remove mandibular bone, the surgeon has the choice of three procedures. The most conservative of these is resection of the cancer along with the underlying periosteum and a superficial plate of bone. Naturally this conservative procedure should be reserved for minimal lesions.

More commonly it is necessary to remove a full thickness segment of the mandible. Segmental resection, as opposed to resection with disarticulation, is the simpler operation; it is less deforming and creates a defect which is easier to repair. Under certain circumstances it will not be curative and the selection of the proper operation is important.

The basic consideration in making this decision is whether or not the mandibular canal with its vessels, nerves, and lymphatics has been entered by cancer cells. This canal begins at the mandibular foramen on the inner surface of the ramus just below the sigmoid notch, traverses the ramus and body of the lower jaw bone, and terminates at the mental foramen on the outer surface near the cuspid region. It forms a natural path of least resistance for cancer dissemination and if invaded any operation other than adequate jaw resection with disarticulation at the temporomandibular joint is likely to leave behind a segment of mandible with cancer growing in its core (Fig. 5).

The surgeon may overlook a common anatomic variation in making this decision. The character of the lower jaw changes rapidly after teeth are lost. This change may be relatively slight after a few extractions or very marked when completely edentulous (Figs. 7 and 8). The mandibular canal is about equally distant from the superior and inferior borders of the *normal* tooth containing mandible. When teeth are lost the mandible becomes smaller. As the alveolar process is absorbed, the mandibular canal remains almost as far from the inferior margin of the jaw as it was originally but may be only a millimeter or so from the superior cortical border. Under this condition almost any erosion from within the

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mouth enters the canal immediately and spreads up and down this pathway (Figs. 3 and 7). As a corollary fact, the mental foramen is no longer on the external surface but opens on the superior surface at submucous depth and carcinoma of the lower labial and buccal sulcus arises almost in contact with the opening (Fig. 8). Slight penetration places the cancer cell in such a position that the mandibular canal must be considered as invaded by means of this foramen, and, even though x-ray examination does not reveal a destructive process, resection and disarticulation of the ipsilateral jaw are indicated.

Advanced or recurrent carcinoma of the lip often spreads to the region of the mental foramen with direct invasion and subsequent rapid ascent of the mandibular canal. In such cases local and cervical lymph node control may be accomplished only to find cancer actively progressing in the core of the mandible unless this is included in the plan of treatment (Fig. 5).

Certain facial or intraoral primary cancers metastasize to the upper cervical lymph nodes. Cancer of the lip characteristically metastasizes first to the buccal node which is adjacent to the lower border of the mandible at the point where it is crossed by the facial artery. These nodes become fixed to the periosteum early and then invade the jaw from below just as the intraoral growth may from above (Figs. 2b and 4). The same principles of treatment hold. The mandible must be resected and disarticulated on this side if there is likelihood of mandibular canal invasion. Lesser penetration still demands bone excision. When bone erosion is obvious on x-ray examination its actual extent is greater than shown.

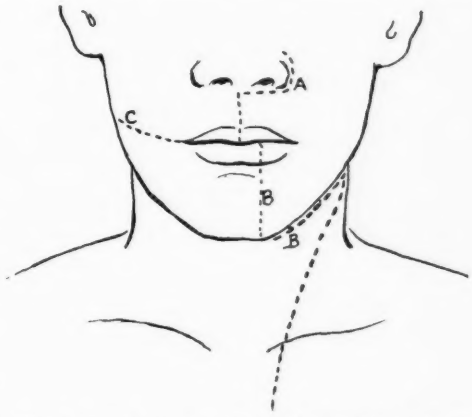
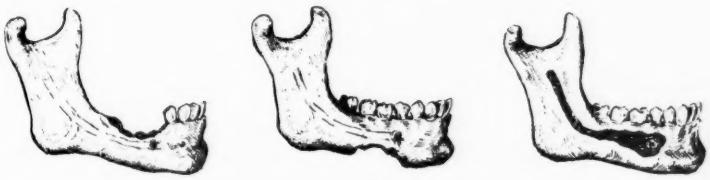


Fig. 1. Good access to the mouth makes for a cleaner operation and minimizes the possibility of fragmentation of the tumor with seeding of implants on to receptive raw surfaces. Incision *A* is helpful in reaching lesions of the upper jaw and antrum. Incision *C* may give exposure if the mouth is small because of scarring from previous treatment. *B* indicates a line of incision through the lower lip at a suitable point. It joins the transverse limb of the neck dissection incision, permits the cheek to be reflected, and gives good access to the mouth for combined neck and intraoral operations.

Full thickness mandibular resection is performed in conjunction with a neck dissection. This dissection is usually complete. It is not infrequent to find that an otherwise good result has been ruined by the development of



a b c

Fig. 2. a, The most frequent route of invasion of the mandible by cancer is from direct extension of the intraoral primary lesion. The mandibular canal may be from 1 to 15 millimeters deep from the oral border of the mandible, depending upon the degree of bone absorption if the mandible is edentulous. Mandibular canal invasion requires treatment by disarticulation. Lesser erosion can be treated adequately by local bone removal or segmental resection. b, The second most common route of invasion is direct extension of the cancer from involved lymph nodes of the upper neck. The distance of the mandibular canal from the lower mandibular border changes little in the older patient (Fig. 7). c, Cancer of the lip or lower buccal sulcus enters the mental foramen directly and extends up the mandibular canal when the primary growth is adjacent to the foramen. Treatment requires resection with disarticulation. See Figure 8 for variations in the position of foramen.

Fig. 3.

Fig. 4.

Fig. 5.

Fig. 3. Black object is lead shot coincidentally present which serves to mark the point of cancer invasion of the mandible into the superficially located mandibular canal. This mandible must be resected and disarticulated on this side to avoid leaving cancer behind in the core of bone which would remain if the mandible simply had a segment excised. (Illustration supplied by Dr. Frank McDowell.)

Fig. 4. Lower border of mandible has been eroded away by cancer extending from an attached lymph node. Metastases from cancer of the lip most frequently cause this type of destruction. If the mandibular canal has been approached the mandible must be resected and disarticulated on this side.

Fig. 5. Roentgenogram of half a mandible containing cancer removed at operation. When first seen, the patient had recurrent carcinoma of the lip extending to within a few millimeters of the mental foramen. At that time x-ray films of the mandible did not reveal bone destruction. Operation consisted of removal of the primary lesion and neck dissection in continuity. Resection and disarticulation of the mandible were considered but not done because the growth was not applied directly to the foramen. Microscopic examination of soft tissue specimen from the operation taken immediately adjacent to the foramen did not reveal tumor. Several months later the patient complained of pain and the mandible as shown was removed. Otherwise the cancer appeared controlled. This pattern of spread through the mental foramen and up the mandibular canal has been repeatedly observed. Persistence within the remaining mandibular canal has been noted after conservative bone resection.

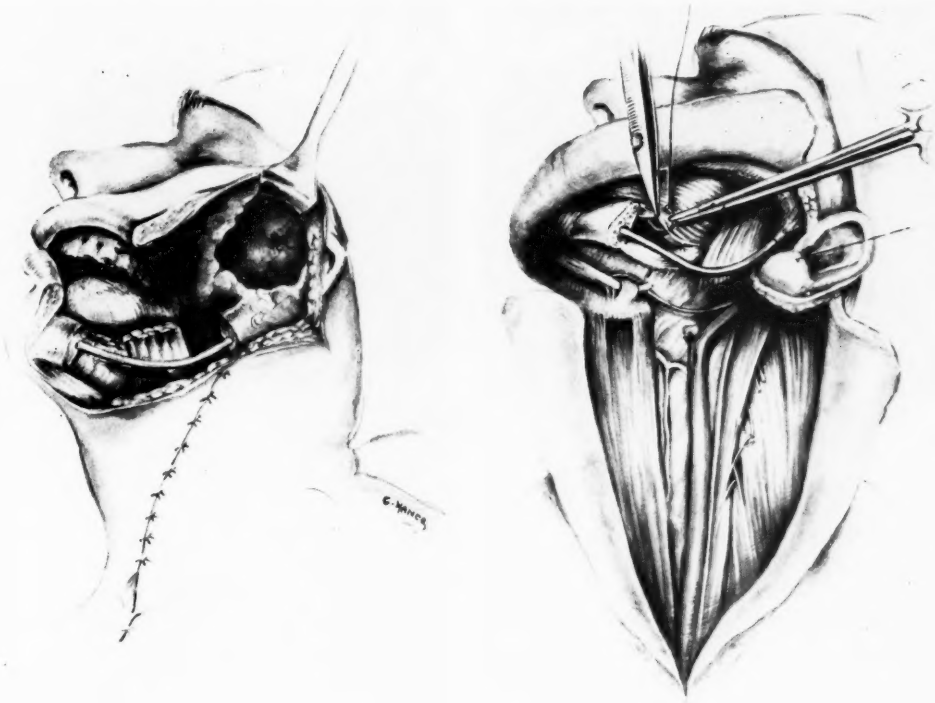
metastatic cancer inferior to a previously performed limited dissection. The operation consists of removal of node-bearing tissue of the neck and the primary lesion of the mouth in continuity. The full thickness of the cheek or other tissues are removed if necessary.

Free access to the mouth is obtained by additional incision and cheek reflection in most cases. The primary cancer is such that it may be easily fragmented and receptive surfaces can be seeded with implants. The possibility is diminished by good exposure (Fig. 1).

Interruption of mandibular continuity permits collapse of the pharyngeal funnel with attending respiratory and early and late nutritional problems. These complications may be minimized by immediately controlling the remaining jaw fragments, holding them in as near normal anatomic relationship as possible. Certainly the assurance of an open airway is of primary concern and occasionally the performance of a tracheostomy is necessary. If there is any question as to its necessity this is mandatory. However, this is not necessary as a routine procedure and may add to the hazard of treatment. Proper attention to mandibular support usually suffices.

PRESERVATION OF ORAL AND PHARYNGEAL SUPPORT

As soon as the resected tissue has been detached and bleeding controlled, mandibular continuity and support are secured. Usually skin flaps have been sutured to cover the



a b

Fig. 6.

Fig. 6. a, Drawing of method of restoring mandibular rigidity and support after segmental resection (see Fig. 9). b, Method of using prosthesis illustrated in Figures 11 and 12 after the mandible has been resected and disarticulated. This type of prosthesis is used only where there is good soft tissue covering both inside the mouth and out and when there is some hope of permanency and repair. See text.

Fig. 7. a, Segments of mandible from 2 adults, one with average dentition, the other edentulous. The mandibles have been cut to permit exposure of the mandibular canals through which a lead wire has been passed. Although cadaver mandibles, the remnants of nerve present permitted accurate positioning of this wire. Note that while the canals in the two specimens were nearly equidistant from the lower borders of the bone, the depth on the superior surface in the edentulous jaw was slight and that even superficial erosion would have entered the channel. b, Cut ends of sections of mandibles described above.

Fig. 8. Two complete adult mandibles photographed to show the great variation in the accessibility of the mental foramen to cancer invasion. In the edentulous mandible, a, the foramen is almost on the superior border and would be submucous in position in the living patient. Carcinoma of the alveolar mucosa over this has a natural path of entrance and the mandible should be resected and disarticulated. In mandible, b, the foramen is more protected.

a b

Fig. 7.

a b

Fig. 8.

Fig. 9.

Fig. 9. Roentgenogram of simple internal bar fixation illustrated in Figure 6a. Note that portion of bar inserted into bone is bent so that natural pressures are not exerted on the ends of the bar but are taken by the surface of a bent segment. This prevents the gradual penetration of the bone by the end of the bar.

a

b

Fig. 10.

Fig. 10. a, Photograph with mouth open and closed taken 3 weeks after complete neck dissection with disarticulation of the mandible after resection in the cuspid region. The primary lesion involved tongue border, floor of mouth, alveolar mucosa, mandible, and attachment of anterior tonsillar pillar. All tissue was removed in continuity. Tracheostomy was not done. b, Roentgenogram showing the internal prosthesis still in place. This consisted of a threaded Kirschner wire drilled into the mastoid tip behind and snugly fitted into a hole drilled into the cut end of the mandible in front. This wire was exposed inside the mouth because there was insufficient soft tissue to cover it. It was removed as a very simple procedure at 4 weeks after operation having accomplished its purpose.

lower neck wound in the interest of asepsis before the mouth is opened.

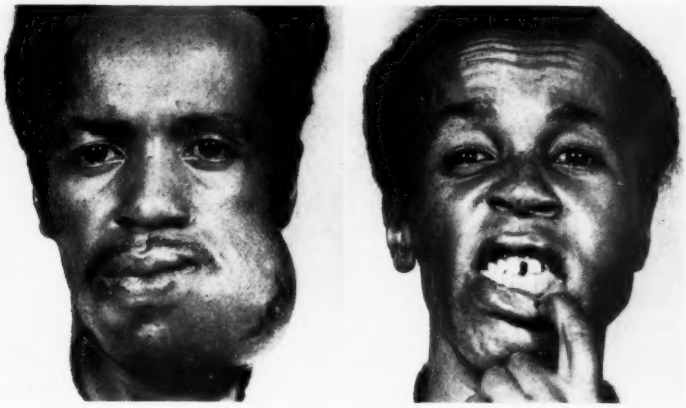
If a simple segmental resection of the mandible has been done the procedure is simple. The gap is bridged by the insertion of a bar of stainless steel of appropriate length between the bone ends. The most dense bone is drilled and the bar inserted snugly into the drill holes in the ends of the bone (Fig. 6a). If this bar is inserted so it is straight and in line with the mandible it will continue to penetrate the bone and eventually telescope. In the average case the resected segment is long enough that ramus must be united to the symphysis or a point near it. This procedure permits the bar to be bent at the ends and inserted so that the portions contained within the bone are not in a straight line with the part bridging the gap between bone ends. Thus, the stress is distributed so the metal ends stop boring through the rather soft bone (Fig. 9).

This method of fixation is simple and the prosthesis is easily tailored to fit. No effort is made to shape the bar to conform to the normal curvatures of the mandible. Rather the prosthesis follows the straightest line between the two points and is so placed that it will lie between inner and outer soft tissue covering without pressure on either. Soft tissue covering such a metal prosthesis under tension will usually be cut through eventually. As secure a closure of intraoral tissue is made as possible. The overlying skin is closed with dependent drainage.

The material used should be of inert metal which can be bent and cut easily with ordinary wire pliers and cutters at the operating table. As its function is to maintain the distance between the bone ends and to prevent uncontrolled motion it must be of adequate caliber and rigidity. Certain disadvantages arise from the use of too great thickness.

FATE OF THE PROSTHESIS

The purpose of the internal support is to make the patient's postoperative course as



a b

Fig. 11.

Fig. 11. a, Type of patient in which more permanent form of internal prosthesis can be used after disarticulation of the mandible. This is a benign tumor following the removal of which adequate soft tissue will remain to supply good coverage of the prosthesis. A bone graft can be inserted after healing is complete, leaving the prosthesis in place and using it as a splint for the bone graft. b, Photograph taken after the prosthesis has healed in place, showing good occlusion of the remaining jaw. See Figure 6b and Figure 12 for details of prosthesis and its insertion.

Fig. 12. Photograph of prosthesis used in patient shown in Figure 11. Its advantages are that it is simple and adaptable and can be tailored to meet the problem at hand with sterile wire pliers and cutter. It is used only where some permanency and repair are intended. The weakness of the scheme is that inadequate soft tissue to supply coverage often remains after a cancer operation. A more bulky prosthesis has less chance of permanency. The roentgenogram illustrates prosthesis in place in patient shown in Figure 11.

Fig. 12.

easy as possible by enabling him to eat and breathe easier and to reduce pain from movement of bone fragments. It also holds the bone ends apart during the healing period so that the final displacement is less. In most instances it is a temporary splint which is removed after 2 to 6 weeks. In some cases the metal bar has become permanent. The degree of permanence depends largely upon the conditions present at the end of the operation.

After completion of an adequate cancer operation sometimes so much skin or mucous membrane has been removed that the metal bar is exposed on the inside of the mouth, on its outer surface, or both. Here its removal is simple after the purpose has been achieved. The bar is cut in the middle and the two ends withdrawn. Under such conditions the prosthesis could not become permanent.

Often intraoral covering can be secured by elevating the floor of the mouth and sufficient skin is present. Frequently the bar will heal in and function perhaps for months until it gradually works loose. It can be exposed through a small incision, divided, and withdrawn. It is desirable that the caliber and temper of the bar used be such that it can be cut with a simple pointed wire cutter, other-

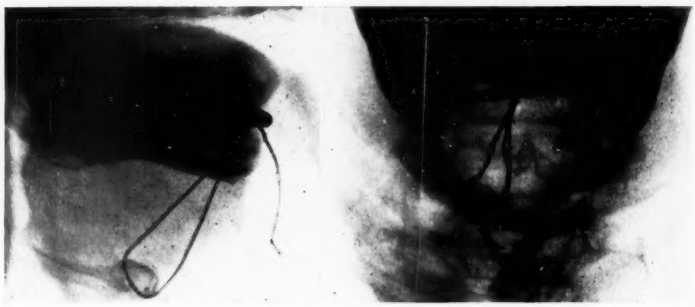


Fig. 13. Internal bar fixation with attached circumferential wire passed around hyoid bone after resection of the symphysis. By stabilizing bone fragments and holding hyoid in normal position tracheostomy may often be avoided.

wise a more cumbersome compound instrument must be used and a larger incision made to permit its introduction. A suitable size of Kirschner wire can serve as the prosthesis.

In a few instances following cancer operations the internal support has healed in place and several months later a bone graft has been inserted to bridge the space preserved by the prosthesis. No splint or appliance other than the bar has been necessary for fixation. A deficiency of soft tissue to house the graft may prevent this type of repair.

The internal prosthesis may be invaluable after the resection of the mandible for benign tumors. Subperiosteal resection in two 9 year old children was performed in 1943 and an internal prosthesis inserted[1]. The mandible regenerated and has kept pace with the normal in growth. The bar is still in place and not causing symptoms 10 years later. A number of adults have had bone grafts applied a few months after mandibular resection and internal prosthesis for treatment of benign tumors, the prosthesis acting as a splint for the graft.

If a resection of the mandible with disarticulation at the temporomandibular joint has been done the problem of internal splinting is more difficult. If it is believed that the splinting is definitely to be temporary a threaded Kirschner wire is used. One end is drilled into the mastoid process posteriorly. The threads grip the bone and prevent slipping. The anterior end is inserted snugly into a hole drilled in the cut end of the mandible. Such a prosthesis gives good mandibular support, permits mouth opening because of its flexibility, and is tolerated comfortably (Fig. 10). No such support has been left in longer than 6 weeks because of fear that it might progressively penetrate into deeper dangerous areas. Occasionally, especially after operations for benign tumors, a more permanent type of prosthesis is used in the hope that a bone graft can be done eventually using the prosthesis for its splint. It consists of a slender stainless steel bar with a perforated olive tip on one end which is sutured into the glenoid fossa. The other end is bent with pliers and inserted into the mandibular fragment while the precautions previously described are observed. In order to be successful, adequate soft tissue covering inside and out must be available. Such a prosthesis is more difficult to remove if necessary than is a simple bar because the perforations of the olive tip attach it firmly to soft tissue (Figs. 6b, 11, and 12).

Resections of the symphysis produce a critical situation. The hyoid bone drops downward and backward, and anchorage of structures essential to the airway is lost. It is desirable that the mandibular segments be maintained in their normal relationship. The insertion of an internal bar, to preserve this space, and attachment of the hyoid bone to the center of the bar by means of a circumferential wire are sometimes essential for immediate free respiration and eventual repair if indicated (Fig. 13).

[1]Byars, Louis T. Subperiosteal mandibular resection with internal bar fixation. Plastic & Reconstr. Surg., 1946, 1: 236–239.

PAPILLARY CYSTADENOMA LYMPHOMATOSUM

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PAPILLARY cystadenoma lymphomatosum was recognized as a distinct anatomic variation in 1910 by Albrecht and Arzt. Early articles suggest that this lesion is a rare tumor of salivary glands. Members of the Mayo Clinic who reviewed the parotid tumors observed between 1907 and 1944 listed papillary cystadenoma lymphomatosum as occurring in 2 per cent of the 909 cases reviewed (3). In 1950 Thompson and Brunt collected 163 acceptable cases from the literature and added 17 of their own to make a total of 180 cases.

Twelve cases that are histologically similar have been collected from the files of Passavant Memorial Hospital between June, 1942 and June, 1953. Thus it would seem that this lesion is not so infrequently seen as the literature would suggest. Perhaps other institutions have similar entities in their files and have not reported them.

SUMMARY OF CASES OF PAPILLARY CYSTADENOMA LYMPHOMATOSUM

CASE 1. L.W., 6-4-42, age 42 years, female, white, swelling on right side of face over parotid area; 1.5 centimeters in diameter, hard, freely movable, duration 1 year. No pain.

Gross examination: tissue is firm, 3 by 3 by 1.5 centimeters, encapsulated, gray to pink, and cystic.

CASE 2. M.C., 12-26-44, age 67 years, male, white. Nodule on right side of face over parotid area; 3 centimeters in diameter, firm, somewhat fixed, duration 5 years. No pain.

Gross examination: tissue is firm, 4 by 3 centimeters, encapsulated, and red.

CASE 3. L.C., 11-26-47, age 51 years, male, white. Mass on left side of face over parotid area, 1 centimeter in diameter, soft, attached, duration several months. No pain.

Gross examination: tissue is firm, 3 by 0.5 centimeters, encapsulated, light tan, and cystic.

CASE 4. M.M.L., 3-9-50, age 46 years, female, white. Nodule on left side of face over angle of jaw, 2 centimeters in diameter, attached, duration several months. No pain.

Gross examination: tissue is firm, 1.5 centimeters in diameter, encapsulated, and tan.

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CASE 5. I.L., 11-18-50, age 47 years, female, white. Swelling on right side of face over angle of jaw, 2 centimeters in diameter, not hard, freely movable, duration 4 years. No pain.

Gross examination: tissue is firm, 3.1 centimeters in diameter, encapsulated, pink to tan, and cystic.

CASE 6. H.W.H., 1-21-51, age 68 years, male, white. Mass on left side of face over angle of jaw, 2 centimeters in diameter, firm, not attached, duration 5 years. No pain.

Gross examination: tissue is soft, 2.1 by 1.8 by 1.4 centimeters, encapsulated, gray to pink, and cystic.

CASE 7. H.J., 4-11-51, age 59 years, male, white. Growth on left side of face below and anterior to the ear, small, disappears on pressure, duration 4 months. No pain.

Gross examination: tissue measures 2.5 by 1.9 by 0.5 centimeters, is encapsulated, tan to gray, and cystic.

CASE 8. E.E., 7-18-51, age 61 years, female, white. Swelling on left side of face, 3 centimeters in diameter, movable, duration 6 months. No pain.

Gross examination: tissue is firm, 3 by 2 by 0.6 centimeters, encapsulated, brown to gray, and cystic.

CASE 9. B.M., 9-12-51, age 35 years, male, white. Tumor left side of face over parotid gland, 1 centimeter, firm, and movable. Duration a few weeks. No pain.

Gross examination: tissue is soft, 2.5 by 2 by 1.5 centimeters, encapsulated, pink to gray, and cystic.

CASE 10. L.H., 4-29-53, age 58 years, male, white. Mass on left side of face over angle of jaw, 6 centimeters in diameter, spongy, and movable. Duration 6 weeks. No pain.

Gross examination: tissue is soft, 4 by 2.2 by 2.2 centimeters, encapsulated, gray and red, and cystic.

CASE 11. H.C., 5-22-53, age 68 years, male, white. Swelling right side of face below mandible, 4 centimeters in diameter, hard, movable. Duration 6 years then 6 days. No pain.

Gross examination: tissue is firm, 4 by 3.5 by 3 centimeters, and brown to yellow.

CASE 12. V.C., 6-11-53, age 75 years, female, white. Growth on left side of face over parotid gland, size of small orange, firm and attached. Duration 6 years, tender past 6 days.

Gross examination: tissue is firm, 3.5 by 3.5 by 3 centimeters, red, gray and tan, and cystic.

The photomicrographs (Figs. 1 to 6) are representative of the type of lesion present in all the cases.

DISCUSSION

A number of names have been suggested for this lesion. Without indicating that one is

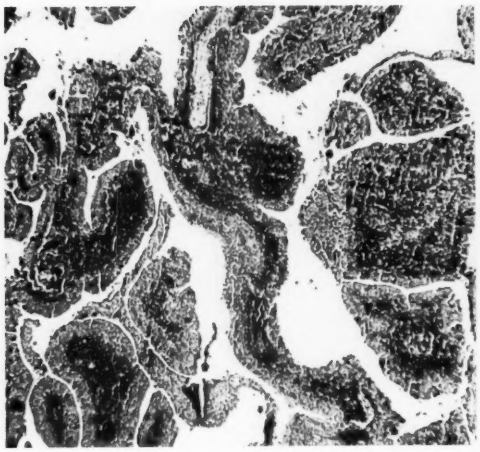

Fig. 1. Photomicrograph of lesion present in Case 2. ×54.

Fig. 3. Photomicrograph of lesion present in Case 6. ×54.

better than another, and realizing that papillary cystadenoma lymphomatosum is a descriptive name, it is appropriate to simplify the terminology and adhere to it.

The general features of the lesion have been well outlined by earlier writers. To repeat them is unnecessary, except to note a few variations in this series.

The youngest person in this study was 35 years old (Case 9, B.M.). Though below the age group of 45 to 70 years, this is not the youngest recorded case. The average age for this group, 56.4 years, corresponds with the average age of 56.3 years as reported by Carmichael, Davie, and Stewart.

Fig. 2. Photomicrograph of lesion present in Case 4. ×54.

The preoperative duration of the mass, as listed in other case histories, is variable, ranging from 8 weeks to 30 years. The shortest history in this group was 6 weeks, and the longest was 6 years. One member of the group (Case 11, H.C.) had noticed a mass below the mandible for a period of 6 years. Then, during a period of 6 days prior to surgery, the area enlarged to the size of an "orange." This is an interesting feature that leads to speculation whether the lesion is inflammatory, or neoplastic, or a developmental anomaly. Several authors have demonstrated elements of salivary gland epithelium closely associated with lymphoid tissue of adjacent lymph nodes developing in the parotid and submaxillary salivary gland regions during fetal and neonatal life. Sections of adult salivary ducts have shown squamous epithelium lining the ducts near the opening into the mouth. This changes to two layers of cells: an inner composed of columnar, regularly arranged cells, and an outer layer of irregularly spaced cuboidal cells, all of which may be found in the papillary cystadenoma lymphomatosum. During embryonic development, at the time when the capsule forms around the parotid

Fig. 4. Photomicrograph of lesion present in Case 8. ×54.

Fig. 5. Photomicrograph of lesion present in Case 10. ×54.

gland, the areas of lymph tissue develop into parotid nodes, and the salivary gland duct epithelium may be separated from the remainder of the gland. The supporting stroma shows the feature of lymph node, with sinuses, cortex, germinal centers, and capsule. No evidence is found to disprove a concept that the epithelium may not be stimulated to secrete a granular precipitate composed of desquamated epithelium, lymphocytes, phagocytes, fat and cholesterol, or to produce a cystic mass in the heterotopic salivary gland tissue within a period of 6 days. The rate of growth is dependent upon the rate of secretion: the larger the lesion, the larger the cystic spaces. Another interesting feature of this same case was the mixed tumor of the parotid gland that was located beneath the capsule and adjacent to the papillary cystadenoma lymphomatosum. Again, speculation exists as to what influence this tumor may have had to initiate the epithelial cells of the papillary cystadenoma lymphomatosum to secrete the granular precipitate.

The sex ratio in previous reports varies from 7 males to 1 female, to 4.5 males to 1 female. In the group at Passavant Hospital, 7 are males and 5 are females. This is a ratio of 1.4 males to 1 female. Admittedly, this variation may be due to the relatively small number of cases. All of the cases belong to the white race. This may be explained by the fact that the hospital population is predominantly white. In none of the cases was the tumor bilateral. However, a previous review of tumors of the salivary gland lists 1 such case (5).

In none of the cases was there any evidence of malignancy, either histologic invasion or metastasis. The surgical notations made frequent mention of the mass being encapsulated and being removed with relative ease.

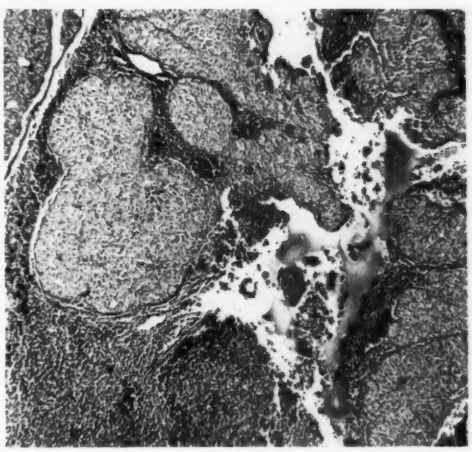

Fig. 6. Photomicrograph of lesion present in Case 11. ×56.

No recurrences have been recorded. A number of the cases are recent surgical specimens and the period of follow-up is short, but if the mass is removed in its entirety, there should be no fear of renewed growth.

This lesion presents itself as one of the painless tumefactions located in the parotid gland usually near the angle of the jaw. The location and characteristics should lead to its consideration in the differential diagnosis of salivary gland enlargements.

SUMMARY

Twelve cases of papillary cystadenoma lymphomatosum are added to those reported previously.

Medical literature suggests that this lesion has characteristics of both an inflammatory and neoplastic process. A further postulation is that it is a developmental anomaly and that heterotopic salivary gland epithelial elements may be stimulated to secrete a granular precipitate.

The lesion is a distinct entity which may be diagnosed preoperatively.

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URINARY AND FECAL INCONTINENCE DUE TO CONGENITAL ABNORMALITIES IN CHILDREN

Management by Implantation of the Ureters into an Isolated Ileostomy

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MANAGEMENT of the patient with both urinary and fecal incontinence presents a challenging problem for the surgeon. Without treatment these people are uncomfortable because of constant soilage and skin maceration. They are malodorous, and therefore socially unacceptable, and are unable to indulge in many of the activities of a normal life. They are frequently severely ill because of urinary infection. Indeed, the eventual outcome in many cases has been almost merciful death from renal failure.

When recently faced with 2 such children the most feasible solution to the problem seemed to us to be the use of the so-called "Bricker procedure" (1, 2) (Fig. 1). In this operation a short segment of terminal ileum is isolated. The proximal end of the segment is closed and placed at the sacral promontory, and the open distal end is led out through the abdominal wall. The ureters are implanted into the proximal portion of the bowel and the isolated ileum then acts as a conduit from the ureters to the skin where the urine can be collected in a skin-adherent ileostomy bag. According to Bricker this procedure was first carried out clinically by Dr. Heinz Hoffner of St. Louis. To our knowledge it has been employed in humans only in those cases in which radical excision of the pelvic viscera was performed. We present our experience in support of the idea that the procedure might have wider application.

CASE REPORTS

CASE 1. A. P., A-5636, was born with the following abnormalities: (1) complete exstrophy of the bladder, (2) unusually wide separation of the symphysis pubis, (3) imperforate anus and rectoperineal fistula, (4) bifid scrotum, (5) bilateral inguinal hernias, (6) spina bifida occulta with a hemivertebral deformity of the third and fourth lumbar vertebrae, and (7) a left congenital club foot.

At 2 months of age the hernias were repaired and then, at a separate procedure, an attempt was made to correct the imperforate anus and fistula. A functioning sphincter was not obtained, probably because of a nerve defect related to the spina bifida.

At 16½ months intravenous pyelography (Fig. 2a) showed a grade 3 ureterectasis and caliectasis with bilateral ureterovesical obstruction. The blood urea nitrogen was 40.0 milligrams per cent. A bilateral ureteroileostomy was then performed after the method of Bricker. The postoperative course was uncomplicated. An intravenous urogram 1 month after surgery showed definite decrease in the dilatation of the right upper tract. Grade 3 dilatation, however, persisted on the left. The exstrophied bladder was removed when the child was 27 months old (10 months after operation) and urograms showed grade 1 dilatation bilaterally. At 30 months (13 months after operation) the urograms (Fig. 2b) were interpreted as essentially normal. At 32 months (15 months after operation) the plasma carbon dioxide combining power was 26.0 milliequivalents per liter (normal 25 to 30 mEq./l.); blood urea nitrogen equalled 17.0 milligrams per cent (normal 20 mgm. per cent or below); chloride equalled 103 milliequivalents per liter (normal 98 to 106 mEq./l.); sodium equalled 142 milliequivalents per liter (normal 135 to 145 mEq./l.); potassium equalled 4.3 milliequivalents per liter (normal 3.5 to 5.5 mEq./l.).

Also at that time an ileogram (Fig. 2b) showed a segment of ileum which irregularly traverses the right lower quadrant of the abdomen. Repeated catheterization of this has shown a residual urine of 0 to 3 cubic centimeters. This would indicate that this segment of ileum acts primarily as a conduit and not as a reservoir, thereby reducing the opportunity for reabsorption and also eliminating urinary stasis and resulting urinary infection.

The skin about the ileostomy has remained clean without ulceration or infection (Fig. 3). The urinary discharge has been managed satisfactorily by the use of a diaper. When the child is older he will be fitted with an ileostomy bag. Fecal incontinence and im-

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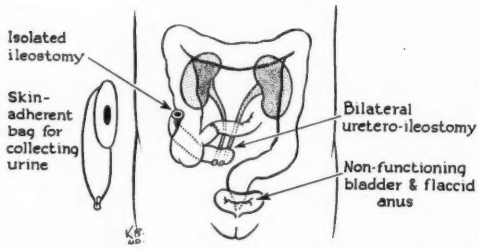

Fig. 1. Outline of the end result of the procedure for urinary diversion described by Bricker. An isolated segment of terminal ileum is used to convey the urine from the ureters at the back of the abdomen to the anterior abdominal wall. Here the urine is collected in a diaper in infancy, and in a skin-adherent ileostomy bag in the older patient.

pactions are now readily controlled by the use of a mildly constipating diet and simple daily enemas.

The improvement in his general condition has been striking. He runs and plays actively with other children and is healthy and happy. There has been improvement in his renal function and urinary tract infection has been absent.

CASE 2. I.A., A-4340, was born with a myelomeningocele which was repaired at the age of 3 months. The child was paraplegic and had bilateral dislocated hips. She had had both urinary and fecal incontinence since birth. The rectal sphincter was flaccid and urine gushed from the urethra on light pressure over the lower abdomen. Chronic and recurring urinary tract infection was controlled at first by gantrisin but finally became resistant to all urinary antiseptics.

At 3 years of age cystoscopy showed a severe cystitis and a neurogenic bladder. An intravenous pyelogram (Fig. 4a) showed grade 3 dilatation of the upper urinary tract. Her blood urea nitrogen was 11.6 milligrams per cent. At the age of 3 years and 4 months the Bricker procedure was performed. The postoperative course in the case of this patient was excellent.

Since surgery she has had no further episodes of chills and fever. A chronic purulent cystitis of the unused bladder persisted for several months but now appears to be controlled. An intravenous pyelogram taken 6 months after operation (Fig. 4b) shows essentially normal kidneys. At the time of writing (9 months following operation) her plasma carbon dioxide combining power is 23.0 milliequivalents per liter; blood urea nitrogen equals 12.0 milligrams per cent; chloride equals 102 milliequivalents per liter; sodium equals 143 milliequivalents per liter; potassium equals 4.7 milliequivalents per liter.

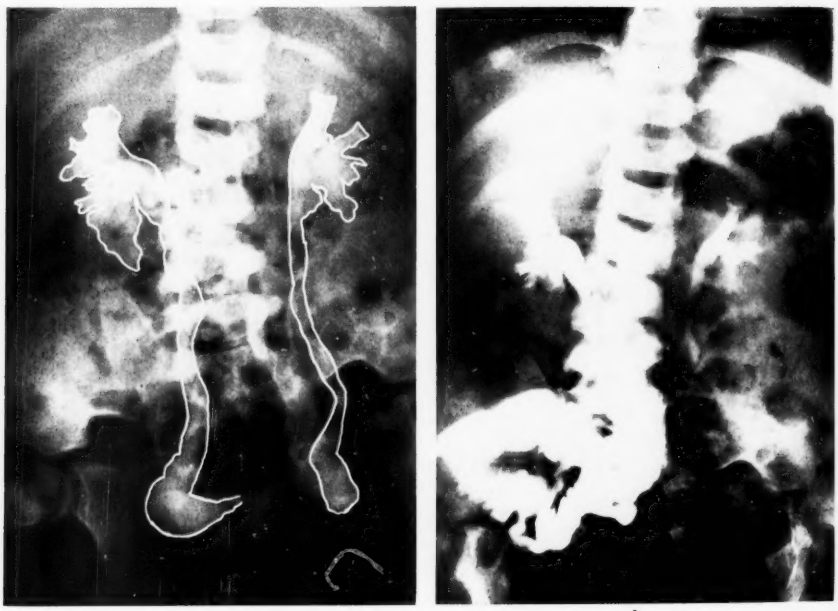

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Fig. 2. Intravenous pyelograms of patient A.P. a, Film taken just prior to surgery at the age of 16½ months. b, Film taken 14 months after surgery to show return of kidneys and ureters to normal. The isolated segment of ileum has also been shown by retrograde injection.

Clinically she has shown no signs of acidosis, and her general growth and development have been normal. Her bowels have been adequately controlled by diet and daily enemas. There has been no skin maceration. Repeated residual urine determinations from the ileostomy have been less than 4 cubic centimeters. Although Escherichia coli have been cultured from the ileostomy on 1 occasion she has shown no signs of upper urinary tract infection.

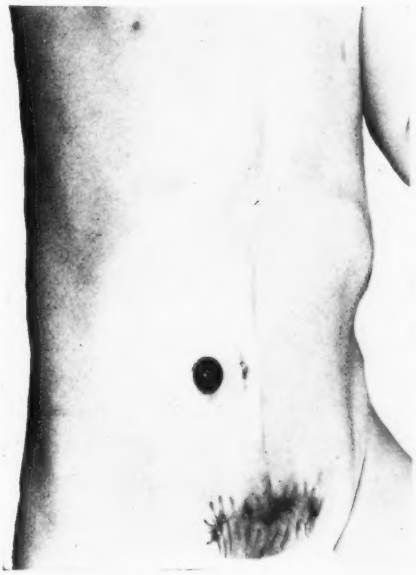

Fig. 3. Photograph of patient A.P. taken 10 months after operation to show position of ileal stoma and absence of skin maceration.

DISCUSSION

In the minds of the authors the chief problem in the management of these patients is to establish some kind of unobstructed urinary flow, and yet one which the patient can easily control. The method selected should not leave the patient susceptible to urinary infection, electrolyte disturbance, or kidney damage. When the fecal control is concerned we, in company with Gross and others, have found that most children with an incontinent anal sphincter can have good bowel control by the use of a carefully followed constipating diet together with regular enemas.

The alternatives which could be considered for urinary diversion include (Fig. 6): (1) bilateral skin ureterostomies or nephrostomies,

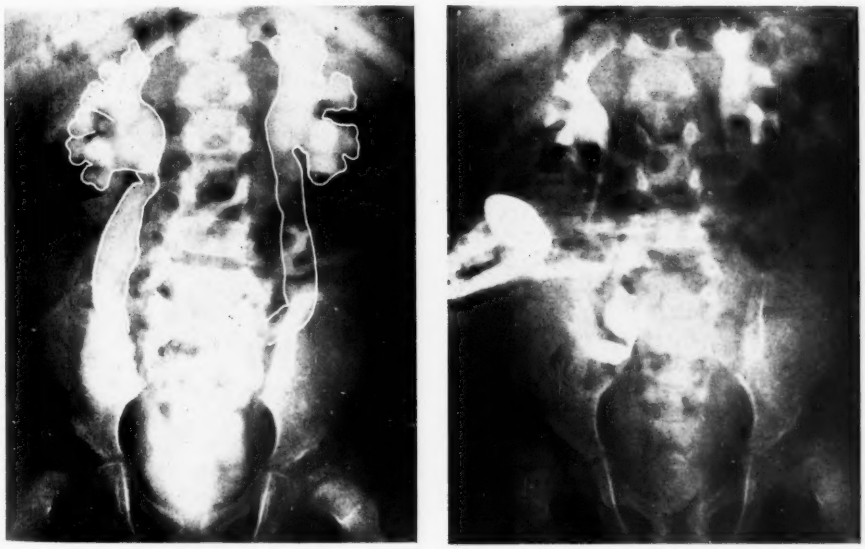

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Fig. 4. Intravenous pyelograms of patient I.A. a, Film before operation to show huge dilatation of kidneys and ureters. b, Film 6 months after operation shows return of kidneys and ureters to normal. The segment of ileum is visualized by retrograde injection of dye.

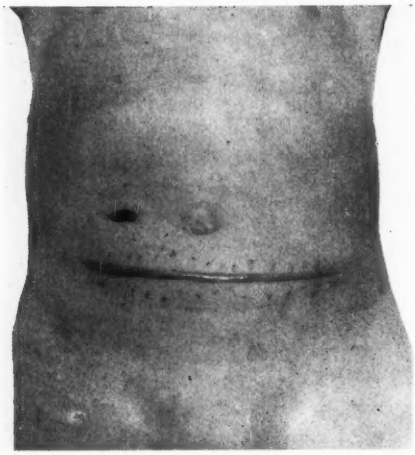

Fig. 5. Photograph of patient I.A. taken 6 months after operation.

(2) a permanent suprapubic cystostomy, (3) "muscle sling" and other urinary sphincter reconstruction procedures, (4) ureterosigmoidostomies with a left lower quadrant end sigmoidostomy (so-called "wet colostomy"), (4) transplantation of the ureters into an isolated pouch of large bowel (i.e., isolated sigmoid pouch or cecal pouch), and finally (6) the use of a segment of ileum as a conduit from the ureters to a collecting bag on the skin (the Bricker procedure).

Of these possibilities bilateral cutaneous ureterostomies require two collecting receptacles, which is inconvenient, and they are also prone to infection, stone, and strictures. A permanent cystostomy has been recommended in the presence of a bladder without sphincter control. Such an arrangement leaves an irritating tube projecting from the bladder with the high probability of continuous infection in the bladder itself and with the likelihood of calculus formation. This method fails to deal with ureterovesical obstruction. Such an arrangement is inconvenient for the patient especially when frequent bladder irrigations and changes of the tube must be carried out. In the absence of a bladder, a cystostomy is obviously out of the question.

Many attempts have been made to create some sort of artificial sphincter mechanism for the bladder but these have been successful in a relatively low percentage of cases.

A wet colostomy has been recommended, but we believe that it will be unsatisfactory largely because of the foul odor from the mixing of fecal and urinary streams and because of ascending infection and pyelonephritis and because of bleeding and stones. Long range follow-up on patients with ureterosigmoidostomies shows a discouraging number of late complications. In the past few years there has been an increasing number of reports of acidosis, hyperchloremia, and hypopotassemia. These findings make one hesitate to employ ureterosigmoidostomy when one is thinking in terms of a full lifetime of palliation. The cause of urinary tract infection and hydronephrosis following ureterosigmoidostomy is explained by some authors on the basis of reflux from the colon and by others on scarring about the site of the ureteral transplant orifices. The reflux has been shown to be the result of the relatively high intracolonic pressure which is present when there is a competent rectal sphincter, and it might be that in the absence of a rectal sphincter, as in a wet colostomy, these complications might not ensue.

Attempts have been made to construct an artificial bladder using a piece of large bowel such as the cecum or sigmoid. Such pouches have been designed to act as reservoirs with a small opening on the abdominal wall, and they are intended to be emptied periodically by passing a catheter through this orifice. The difficulties which have been encountered have been in relation to the size of the opening at the skin, which is liable to be either too large and hence leak, or else too small with retention. This type of pouch is also apt to have spontaneous emptying from peristalsis of the segment of bowel. Calculus formation and rupture of the pouch have been reported. Because of these problems this procedure has not been widely used.

According to more recent theories on the etiology of chemical imbalance following ureterosigmoidostomy one might expect that in those pouches which are continent the complications of acidosis and hyperchloremia might ensue. Peck and Newland report a patient in whom the Gilchrist procedure had

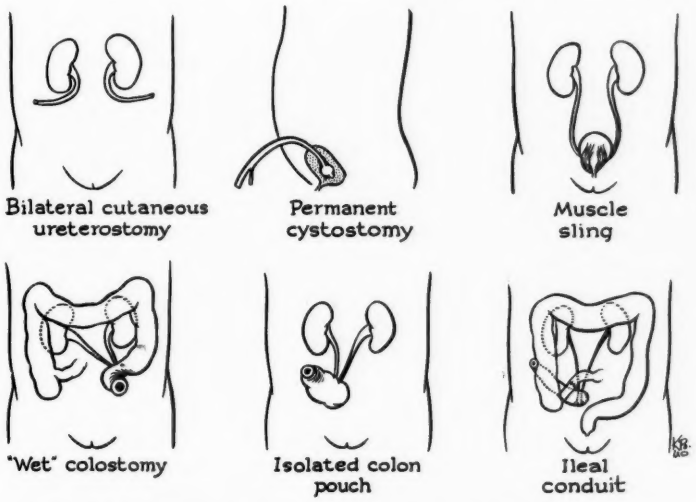

Fig. 6. Schematic drawing illustrating alternative methods for the surgical treatment of urinary incontinence when combined with fecal incontinence.

en done who did develop acidosis (CO_2 qualled 32.2 vol. per cent).

The procedure which we have used in our cases was described by Bricker in connection with patients requiring removal of the bladder and rectum for carcinoma. This method employs an isolated piece of ileum to lead the urine from the ureters out to a position on the anterior abdomen where a plastic easily removable collecting bag can be cemented to the skin. The piece of ileum is not intended to act as a reservoir or artificial bladder but rather as a tube from the ureters to the abdominal wall.

A theoretic objection to this procedure lies in the possibility of excessive absorption of urinary constituents by the segment of ileum. In this regard Rieger and associates have shown in experiments on dogs that an elevated blood urea nitrogen and depressed carbon dioxide are definitely related to the length of small bowel exposed to the urinary stream. Ileal loops greater than 35 centimeters in length were not compatible with life. Mersheimer and associates, using a 10 centimeter length of ileum for bilateral ureteral transplants in dogs, report no evidence of infection and normal pyelography and blood urea nitrogen determinations after an 18 month period of observation. Our ileal segments were 35 and 22.5 centimeters long respectively. We have not found these to be too long as evidenced by the normal chemistries.

The exact mechanism of the blood electrolyte imbalance sometimes found in ureterosigmoidostomies has not been proved conclusively, but there is strong evidence that stasis of urine in the bowel with the absorption of urinary products may be a contributing cause. In addition, according to the work of Lapides and of Creevy and Reiser, renal tubular damage appears to be a significant factor. That stasis has not been present in our cases was demonstrated by the finding of only 4 cubic centimeters of residual urine or less on repeated catheterization of the ileostomies. We believe that the factors of lack of stasis, a short length of bowel, isolation from the fecal stream, and the resiliency of youth have all contributed to the successful outcome in these children.

Our 2 cases have shown gratifying clinical results. Each child has shown marked clinical improvement following the operation. In both cases there was severe bilateral hydro-

nephrosis which subsided following surgery. Each child has been free from urinary infection since surgery whereas before surgery urinary infection was everpresent. Blood urea nitrogen determinations have become normal following surgery in one patient and have remained normal in the other. From the point of view of convenience to the patient and the parents these 2 children have required little extra care. Their diapers are at present worn on the abdomen and skin maceration has not occurred in either case. The manufacturer of the plastic bags is tentatively planning to fit these children with their appliances at 5 years of age.

SUMMARY

The case histories of 2 children with both urinary and fecal incontinence due to congenital abnormalities are presented. The treatment in each instance consisted of transplantation of the ureters into one end of an isolated segment of ileum which was then brought out on the abdominal wall to act as a urinary conduit (the Bricker procedure). The fecal incontinence has been readily handled by a mildly constipating diet and simple enemas.

Previously existing hydronephrosis has markedly improved in each case.

Previously present urinary infection has been eliminated.

The blood electrolyte patterns have been found to be completely normal 9 and 15 months after operation.

This method has provided a socially acceptable, safe, and convenient means of urinary control.

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INVASIVE ADENOMA OF THE THYROID

Analysis of 46 Cases

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WHILE Wegelin (22), Wissmer-Kowarsky, and Ribbert recognized invasion of blood vessels as an important sign of malignant goiter before Graham, it was he who emphasized this phenomenon as the most practical and reliable criterion of malignancy. Graham stated: "It makes very little difference what the tumor looks like under the microscope—whether the cells be large or small, flat, cuboid, or cylindrical, fetal or adult, differentiated or undifferentiated, deeply staining or faintly staining, whether mitoses be abundant or absent, whether there be colloid or absence of colloid, whether the cells be arranged in a single layer or multiple layers in the follicle, whether the follicle wall be thrown into papilliferous folds or not, whether the cells be arranged in follicles, sheets, masses, columns or alveoli, whether the stroma be abundant or scanty, whether degenerative changes be absent or extreme—all of these things are not the most important signs by which to recognize malignancy. The malignancy depends upon the tendency or capacity of the tumor to invade locally, cause local destruction, recur after operation, give distant metastases, and finally to result in the death of the patient."

In Graham's opinion, the most constant single indication of thyroid carcinoma is invasion of blood vessels. Its recognition does not require innumerable blocks for tissue examination or serial section for gross examination. Gross examination of the veins of the capsule and close beneath it will disclose tumor thrombosis or invasion when present. According to Graham, a few blocks through the capsule and adjacent tumor tissue will usually suffice for the microscopic demonstration of vessel invasion. Graham's view of blood vessel invasion as the determining factor in the diagnosis of malignant adenoma has been generally accepted by surgeons and pathologists. Its infallibility has been questioned by only a few investigators. In 1933 Doepfner stated that Graham does not mention the technical details of his histologic studies. He could not find in Graham's paper any data on age, sex, recurrence, or metastases of his 55 cases of adenoma with blood vessel invasion. Doepfner suspected that Graham mistook "intramural growth" of tumor cells in the vessel walls as invasion into the vessel lumen. Doepfner himself, in Wegelin's laboratory, studied 4 adenomas with metastases and 3 proliferant strumas (Langhans). He made 23 to 172 sections from each block and stained every goiter for elastic fibers. Doepfner was able to demonstrate invasion of blood vessels in all cases of metastasizing adenoma. However, in 13 cases of adenoma without metastasis, he found invasion of blood vessels 3 times, also. He furthermore collected 86 cases of invasive adenoma from the literature. Prior to age 20, metastases were extremely rare, and in the first decade of life metastasizing adenomas were never observed. Between the ages of 20 to 40, metastases were uncommon; only in the fifth and sixth decade did they become more frequent. The youngest cases in the literature were those of a 16 year old boy reported by Quensel and of a 17 year old girl observed by Kölichen.

There is a surprisingly small number of papers in the literature on follow-up studies of patients with angioinvasive adenoma. Warren, in 1931, found among 1,114 thyroid adenomas, 34 with blood vessel invasion (3.1 per cent), namely 5 trabecular, 28 small follicular, and 1 unclassified adenoma. These tumors were all in females, and the ages of the patients varied between 24 and 66 years. Thirty-two of the 34 positive cases were followed by Warren. Only 2 patients died of the

TABLE I.—SUMMARY OF DATA

No.	Case	Age	Sex	Clinical symptoms	Duration of goiter years	Preoperative diagnosis	Operation	Weight, and size, gross	Histology	Invasion	Cytologic grade of atypia	Follow-up
1	20946	22	F	Nervous. Incidental discovery	1	Left fetal adenoma	Left lobectomy	42 gm. 5 x 4 cm. Solitary adenoma	Microfollicular	Blood vessels and capsule	1 plus	Unable to trace after 5 years
2	21174	39	F	Nervous. Gradual increase in size of goiter	5	Adenoma of left lobe	Subtotal bilateral thyroidectomy	36 gm. 5 x 3 x 2.5 cm. Multinodular Large node 2.5 cm.	Microfollicular	Blood vessels and capsule	1 plus	Alive and well. Myxedemic 14 yrs. postoperative
3	21248	53	F	Swelling of right neck, 4 years. Rapid increase, 9 months	4	Fetal adenoma, right	Right lobectomy	35 gm. 5.5 x 3.5 x 3 cm. 3 x 2 x 1 cm. Multinodular	Microfollicular	Blood vessels and capsule	2 plus	Unable to trace after 11 years
4	21672	37	F	Nervousness, palpitation of heart	3	Adenoma right lobe of thyroid	Subtotal bilateral thyroidectomy	64 gm. 4.5 x 3.5 cm. Solitary node	Microfollicular	Capsule	1 plus	Living and well 9 years postoperative
5	22837	28	F	Choking sensation, cough, nervousness, heart pounding	1	Large colloid goiter	Subtotal bilateral thyroidectomy	82 gm. 5.5 x 4.5 cm. Solitary node	Follicular, microfollicular, and papillary	Blood vessels and capsule	1	Living and well 11 years postoperative
6	23696	41	F	Nervousness	6	Adenoma of right lobe	Right lobectomy	3.5 x 5.0 cm. Solitary node	Follicular and smallfollicular	Capsule	1	Living and well 12 years postoperative
7	27749	36	F	Nervous, heart pounds, feeling of pressure in neck	2	Adenoma of right lobe	Right lobectomy	28 gm., right lobe. 5 x 4 x 3.5 cm.	Trabecular, large and small-follicular	Blood vessels and capsule	1	Living and well 9 years postoperative
8	25010 25720	50	F	Nervousness, weight loss, palpitation. Recurrent enlargement	1	Bilateral hyperplastic goiter	Right, Jan. 1945. Left, Oct. 1945	24 gm. 6.5 x 4 x 3 cm. Nonencapsulated tumor 10 x 14 mm.	Smallfollicular, few papillary	Blood vessels and capsule	1	Living and well 6 years postoperative
9	25127	25	F	Enlargement of neck of 1 year's duration	1	Adenoma, left lobe	Left lobectomy	28 gm. 5.5 x 4 x 3 cm. One node 4 x 2.5 cm.	Large and small-follicular, few papillary	Blood vessels and capsule	1	Living and well 7 years postoperative
10	25343	31	F	Goiter noticed since abdominal surgery 13 years previously	13	Adenoma, right lobe	Right lobectomy	54 and 57 gm. Rt. lobe 7.5 x 5 x 3 cm. One node 3.5 x 2.5 cm.	Small-follicular	Capsule	1	Living and well 8 years postoperative
11	25427	23	F	Lumps in neck for 10 years	10	Cardiotoxic goiter, second operation	Regional gland removal, x-ray 2. Bilateral thyroidectomy	11 gm. Lateral lobes removed, 2nd operation	Small-follicular	Capsule	1	Living and well 8 years after second operation
12	25625	54	F	Nervousness, loss of weight, short of breath, lump in neck	3	Adenoma of thyroid	Bilateral subtotal	18 gm. 30 gm. Node 3 cm. Rt., 4.5 x 3 x 2.5 cm. Lt., 5 x 2 x 2 cm.	Follicular and small-follicular	Capsule	1 plus	Died 4 years postoperative, without thyroid disease
13	25852	60	F	Nervous, rapid heart, short of breath, weight loss	15	Large adenoma, left lobe of thyroid	Left lobectomy	135 gm., one lobe 8 x 6 x 5.5 cm.	Small-follicular	Not encapsulated	1 plus	Died 2 years after operation
14	25913	62	F	Referred because of enlargement of neck	3	Adenoma right lobe of thyroid	Right lobectomy	40 grams. Solid node	Trabecular and micro-follicular	Capsule	1 plus	Living and well 15 years postoperative
15	25916	54	F	Increasing nervousness, felt that neck was enlarging	15	Adenoma of left lobe	Left lobectomy	24 gm. 5.5 x 3 x 4 cm. One node 3 cm.	Follicular and small-follicular	Capsule	1 plus	Living and well 8 years postoperative

15	25916	54	F	Increasing nervousness, felt that neck was enlarging	15	Adenoma of left lobe	Left lobectomy	24 gm. 5.5 x 3 x 4 cm. One node 3 cm.	Follicular and small-follicular	Capsule	1 plus	Living and well 8 years postoperative
16	25931	25	F	Goiter enlarging rapidly since pregnancy	2	Adenoma of right lobe	Right lobectomy	One adenoma 6.5 x 5 x 5 cm.	Trabecular and follicular	Capsule	1 plus	Living and well 8 years postoperative
17	26342	68	F	Heart pounds	25	Nodular goiter	Bilateral subtotal thyroidectomy	65 and 75 gm. 2 lobes. Rt., 5.5 x 5 x 4 cm. Lt., 4.5 x 3 x 2.8 cm.	Trabecular and small-follicular	Capsule	1 plus	Living and well 7 years postoperative
18	26439	67	F	Headaches, short of breath, rapid heart	42	Adenoma of left lobe	Left lobectomy	18 gm. Node 3 x 2.5 cm. Left lobe 30 gm. 5 x 3.5 x 3 cm.	Follicular, large follicular, and papillary	Capsule	1 plus	Living and well 3 years postoperative
19	27445	21	F	Enlargement of neck	1 mo.	Adenoma of left lobe	Bilateral subtotal thyroidectomy	23 gm. 3.6 x 2.6 x 2 cm. Rt. lobe. Multinodular Lt., 3.3 x 1.6 x 1.5 cm.	Follicular and papillary	Capsule	1 plus	Living and well 6 years postoperative
20	27483	18	F	Swelling of neck for 6 months	6 mo.	Adenoma of left lobe	Left lobectomy	36 gm., tumor 5 cm. Lobe 5.5 x 3.5 x 4 cm. Solitary node	Follicular and small-follicular	Capsule	1 plus	Living and well 3 years postoperative
21	27548	31	F	Nervous, rapid heart, gradual enlargement of neck	10	Adenoma of right lobe	Right lobectomy	150 gm. 8 x 6.5 x 4.5 cm. Whitish node, 15 mm.	Small- and large-follicular	Capsule	1 plus	Living and well 6 years postoperative
22	27552	54	F	Feeling of fullness in throat	3	Colloid nodular goiter, right. Left adenoma	Bilateral subtotal thyroidectomy	107 gm. 8 x 6 x 4 cm., rt. 6.5 x 3 x 2.5 cm., left	Smallfollicular and trabecular	Blood vessels and capsule	1 plus	Living and well 6 years postoperative
23	27675	33	F	Nervous. Rapid heart. Easily upset	5	Adenoma right lobe	Right lobectomy	12 and 18 gm. One node 2.5 cm., cyst 8 x 3 mm.	Small-follicular and trabecular	Blood vessels and capsule	1 plus	Living and well 6 years postoperative
24	28081	25	F	Lump in neck	10 mo.	Adenoma of right lobe	Right lobectomy	18 gm. 2 cm. node with whitish area 6 mm, invading capsule	Trabecular, microfollicular in colloid adenoma	Capsule	1 plus	Living and well 6 years postoperative
25	28281	29	F	Very nervous for several years	5	Adenoma of left lobe	Left lobectomy	22 gms. Large node with small cysts, 6.5 x 5 cm.	Trabecular and smallfollicular in colloid adenoma	Capsule	1 plus	Living and well 4 years postoperative
26	28692	40	F	Lump on right side of neck	5	Adenoma of right lobe	Bilateral subtotal thyroidectomy	30 gm. Two lobes, opaque cyst in left	Macrofollicular and follicular	Capsule	1 plus	Living and well 4 years postoperative
27	28720	24	F	Lump in neck first noticed 6 months previously	6 mo.	Adenoma of left lobe	Left lobectomy	16 gm. 4 x 3.5 x 2.5 cm., node 3.5 x 2.4 cm.	Smallfollicular and follicular	Capsule	1 plus	Living and well 5 years postoperative
28	28872	49	M	Found on physical examination	?	Adenoma of left lobe	Left lobectomy	21 gm., 4 x 3 x 2 cm. Node 3.7 x 2.5 cm., very thin capsule	Trabecular and microfollicular	Capsule	1 plus	Living and well 4 years postoperative
29	28933	35	F	Lump in throat for 12 years	12	Hyperplastic goiter	Bilateral subtotal thyroidectomy	51 gm. Two lobes. Tumor in right lower lobe 3.5 x 3 cm.	Trabecular and small-follicular	Capsule	1 plus	Living and well 4 years postoperative
30	28943	41	F	Nervous, short of breath, palpitation, enlargement of neck	1	Adenoma of right lobe	Adenoma of right, and left lobectomy	64 gms. 6 x 4.5 x 3.5 cm. right 2 x 2.5 x 2 cm. left	Microfollicular and trabecular	Capsule	1 plus	Living and well 9 years postoperative
31	28979	47	F	Discovered during routine physical examination	?	Adenoma of right lobe	Bilateral subtotal thyroidectomy	42 gm. 18 mm. tumor in right lobe, poorly encapsulated	Microfollicular and follicular	Capsule	1 plus	Living and well 5 years postoperative
32	29088	35	F	Discovered lump in neck 2 mo. prior to surgery. Symptomless	2 mo.	Adenoma of right lobe	Right lobectomy	20 gm. Node 3 x 3 cm. Whitish area on one side	Trabecular in periphery of colloid adenoma	Capsule	1 plus	Living and well 4 years postoperative

TABLE I. — SUMMARY OF DATA (CONTINUED)

No.	Case	Age	Sex	Clinical symptoms	Duration of goiter, years	Preoperative diagnosis	Operation	Weight, and size, gross	Histology	Invasion	Cytologic grade of atypia	Follow-up
33	29132	41	F	Nervous, with difficulty in breathing	?	Adenoma of right lobe	Right lobectomy	32 gm. Node 3 x 4 cm., with cysts	Microfollicular	Capsule	1 plus	Living and well 4 years postoperative
34	29502	51	F	Discovered during physical examination	2	Large left adenoma, small right adenoma	Bilateral subtotal thyroidectomy	52 gm.	Microfollicular	Capsule	1 plus	Living and well 5 years postoperative
35	29650	23	F	Patient found nodes in thyroid region self-examination.RN	?	Multiple adenomas of thyroid	Bilateral subtotal thyroidectomy	42 gm. 1 tumor 3x 2 cm. 4 nodes	Follicular in colloid adenoma. Multiple foci	Capsule and blood vessels	2 plus	Living and well 3 years postoperative
36	29685	27	F	Very nervous. Heart pounds	8	Adenomas of the left lobe	Left lobectomy Adenomatous adherent mass	35 gm. Nodular lobe with cyst in upper pole	Macro-microfollicular, papillary	Capsule	1 plus	Living and well 3 years postoperative
37	29706	43	F	Nervous, heart beats fast. Goiter checked elsewhere	?	Bilateral nodular goiter	Bilateral subtotal thyroidectomy	24 gm. Two lobes with 5 mm. node left and two nodes right, 18 and 13	Follicular, macrofollicular and papillary	Capsule	1 plus	Living and well 3 years postoperative
38	30493	70	F	Short of breath. Knot in neck. Epigastric pain	1	Adenoma left lobe	Left lobectomy	18 gm., two nodes 2.8 cm. and 2 cm. One lobe, 3.5 x 3 x 2 cm.	Follicular and small-follicular	Capsule	1 plus	Living and well 2 years postoperative
39	30679	73	F	Nervous 6 months. Goiter 19 years. Speech bothering	20	Colloid goiter with adenoma partially intrathoracic, left	Bilateral subtotal thyroidectomy	176 gm. 6 x 6 cm. node on cross section. 14 and 11 mm. nodes	Trabecular	Capsule and blood vessels	1 plus	Living and well 2 years postoperative
40	30970	23	M	Choking sensation. Marked tremor	4	Adenoma, right lobe	Right lobectomy	4 gm. Node 4.5 x 3 cm.	Trabecular and microfollicular	Capsule and blood vessels	1 plus	Living and well 2 years postoperative
41	31403	28	F	Lump in neck enlarging. Some nervousness, choking	2	Adenoma, right lobe	Right lobectomy	22 gm., right lobe 5 x 3.5 x 2 cm. Node 2.8 x 2.2 cm.	Trabecular	Capsule and blood vessels	1 plus	Living and well 2 years postoperative
42	31527	41	M	Nervousness, neck enlarging for 2 years	6	Adenoma of right lobe	Right lobectomy	20 gm. 4 x 3 x 2.5 cm., node 3.5 x 2.7 cm.	Small alveolar and trabecular	Capsule	1 plus	Living and well 2 years postoperative
43	32742	65	F	Choking sensation. Scratching sensation in throat. Wt. loss	1	Nodular goiter	Bilateral subtotal thyroidectomy	31 gm. Multiple nodes, 1 grayish node in lower pole	Microfollicular and trabecular	Capsule	1 plus	Living and well 1 year postoperative
44	33177	39	F	Weight loss. Has to clear throat always. Very nervous	24	Adenoma of right lobe	Resection of adenoma in isthmus	10 gm. 4 x 2.3 x 2 cm. Node 2.5 x 2 cm.	Trabecular	Capsule	1 plus	Living and well 2 years postoperative
45	34049	18	F	Enlargement of neck. Somewhat nervous	2 mo.	Adenoma of right lobe	Right lobectomy	20 gm. 4 x 3 x 2 cm.	Trabecular, microfollicular, macrofollicular	Capsule	1 plus	Living and well 6 months postoperative
46	34132	58	F	Enlargement of neck for several years. Weight loss	15	Bilateral nodular goiter	Bilateral subtotal thyroidectomy	70 gm. 4.5 cm. node in left lobe, 2.5 cm. right	Smallfollicular, trabecular, and papillary	Capsule	1 plus	Living and well, less than 1 year

lisease, one with lung metastases and the ther with metastases in bones.

While finding of blood vessel invasion in iopsy specimens does not necessarily indicate uture metastases, on the other hand, the bsence of blood vessel invasion, even in serial ections, does not guarantee a benign clinical ourse. Langhans, in his classical paper on the pithelial types of malignant goiter, observed s the most reliable sign of malignancy an invasion of tumor cells through the capsule into he adjacent thyroid tissue, while he saw blood essel invasion only rarely. Of a metastasizing denoma in a 38 year old man he examined rom 250 to 400 microscopic sections, but did ot find invasion either into blood or lymph essels. Also in a Hürthle cell tumor which ad spread to lung, liver, cervical, and bronhial lymph nodes he could not demonstrate nvasion of blood vessels, in spite of examinaion of many sections.

Pemberton states, from his vast experience ith adenocarcinoma in adenomas, that vasular invasion is not necessary to make a istologic diagnosis of malignant goiter; with Broders, he relies rather on cellular dedifferntiation and the presence of mitoses. After tudying goiter material of the Mayo Clinic, Smith contends that the nucelolar-nuclear ratio is a more reliable sign of malignancy than blood vessel invasion.

Wegelin (23) agrees with Graham that invasive adenomas show no difference from benign goiter as to character of cells, the presence or absence of mitoses, colloid content, or the structure of the follicles. Zimmerman points out that the usual histologic criteria of malignant growth—cellular proliferation, irregularity in size, shape, and staining quality of the cells, and frequency of mitoses—may be seen in benign goiter as well, especially following thiouracil medication.

Cohnheim, whose classical case of "benign metastasizing colloid adenoma," according to Simpson, started the literature on invasive adenoma, stated that invasion into blood vessels by itself is not the deciding factor for a malignant course, but that the "constitution" of the patient is a most important factor. Zimmerman believes that there must be a considerable capacity of the blood or tissue to destroy or contain tumor cells. In 19 of 52 malignant goiters, he found blood vessel invasion. Of 15 patients who were followed, only 2 died from their disease, while more patients died from malignant goiter which did not show blood vessel invasion.

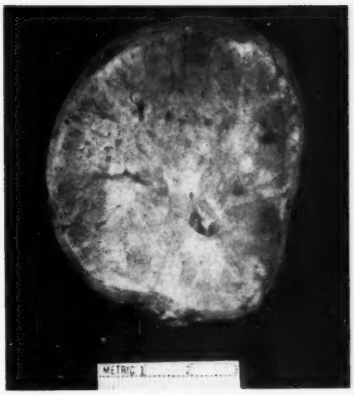

Fig. 1. Case 16. Solitary invasive adenoma of 25 year old female. Goiter enlarged rapidly since pregnancy 2 years ago. Surgical specimen weighed 102 grams. Blood vessels and capsule were invaded by this trabecular and smallfollicular adenoma. The patient is living and well following simple lobectomy.

Of interest is Pool's experience. According to him, the vessel walls of an adenoma are extremely thin as is shown by the tendency to hemorrhage in the central portions. The ap-

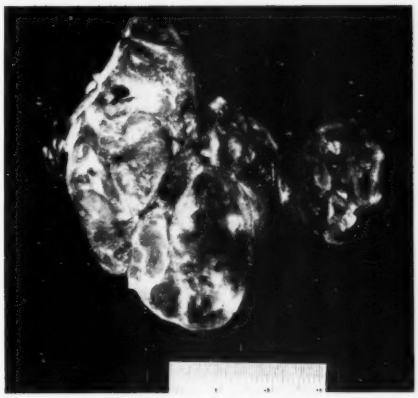

Fig. 2. Case 43. Multinodular goiter, 31 grams, in 65 year old female who complained of choking sensation and weight loss for 1 year. One of the adenomas had invaded the capsule. Patient is living and well following bilateral thyroidectomy.

Fig. 3. Case 10. Solitary invasive adenoma in 31 year old female, noticed for 13 years. The weight was 57 grams. The patient is well, 8 years after right lobectomy.

parent presence of tumor tissue within vascular spaces might represent nonmalignant extension or might be an artefact due to handling or cutting the tissue. Invasion of the vessel wall itself or growth of tumor cells along the intima should be clearly demonstrated before making a diagnosis of blood vessel invasion. Willis stated that tumor cells in blood vessels are not equivalent to metastatic spread. Saphir's autopsy studies of breast cancer, in which he found tumor thrombi in the lung vessels not producing metastases, indicate that most tumor cells carried in the blood stream to distant organs perish, and only occasional cells survive and start metastatic growth. From the study of the literature it appears, therefore, that vascular invasion is not such an infallible sign of malignancy as Graham believed. Our own studies of malignant adenoma seem to support Langhans' view that invasion of the capsule and surrounding thyroid tissue is a more reliable criterion of malignancy than vessel invasion.

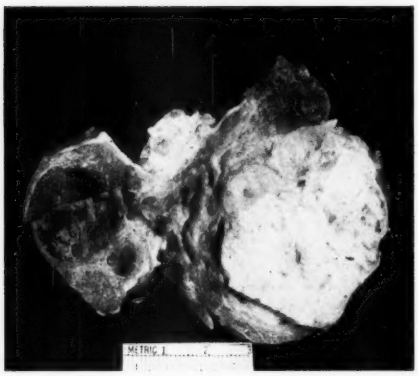

Fig. 4. Case 17. Multinodular goiter in 68 year old female. The patient knew of her goiter for 25 years. The large adenoma in the right lobe invaded the capsule. The patient is living and well 7 years postoperative.

PRESENTATION OF DATA

The data are summarized in Table I.

Sex and age. Forty-three cases were observed in females and 3 in males. The ages of our patients ranged from 18 to 73 years of age at the time of operation. The average age of the female patient was 39.1 years and that of the males 37.7 years.

Clinical symptoms and duration of disease. The patients had noticed enlargement of the neck for from 2 weeks to 52 years; the average duration of the goiter previous to operation was given as 7.2 years. Besides enlargement of the neck, which was the chief complaint of most patients, 6 had noticed definite loss of weight, 2 shortness of breath, 2 had choking sensation, 1 had cough, and 5 had noticed a rapid increase in the size of a long-standing goiter. The most frequent clinical diagnosis was solitary adenoma, while in only 2 cases was cancer suspected. A clinical diagnosis of exophthalmic goiter was made in 2 cases and of toxic nodular goiter in 1 case. Five patients were diagnosed as nodular colloid goiter. Nine patients received Lugol's solution preoperatively, and 2 received propylthiouracil in addition to iodine.

Operation. Bilateral subtotal resection was performed on 17 patients, and lobectomy in 29 cases. In no instance was radical neck dissection performed, neither was isotope treatment administered. Only 3 patients had postoperative x-ray therapy.

Gross pathology. The weight of the surgical specimens varied between 11 and 318 grams. The average weight was 55.4 grams. Twenty-six goiters weighed less than 50 grams, 14 weighed between 50 and 100 grams, 2 specimens between 101 and 150 grams, and 4 weighed more than 150 grams. In 31 cases a solitary node was found, in 9 two nodes were

resent, and in 6 there were multiple nodules involving the whole lobe.

In 14 instances the nodes were less than 2 centimeters in diameter, in 15 instances from to 4 centimeters, 13 were from 4 to 6 millimeters, and 4 measured 6 to 9 centimeters in size. The cut surfaces of the solid tumors varied from opaque, brain-like gray to amber translucent. A central hyaline scar so characteristic of fetal adenomas was seen in only 2 tumors. Cystic areas were present in 13 nodes, hematomas in 12 nodes. The capsule was grossly invaded in 18 cases. Calcification was found only once.

Microscopic findings. Twelve adenomas were uniform in structure. Of these 12, 2 were composed of solid trabeculae, 8 were microfollicular, 1 follicular, and 1 was macrofollicular. All others had pleomorphic arrangement of the cells. Most common (12 times) was a combination of trabeculae and smallest follicles; 7 times microfollicular and macrofollicular structures were noticed. The other 11 presented two or three different structures. In adenomas, occasional papillary proliferation of the follicle wall was noticed.

Table I shows the histologic grade of malignancy. Mitotic figures, oversized nuclei and nucleoli, and variation in size and form of cells were our criteria of anaplasia. All but 2 of our specimens were of a grade 1 malignancy. The great majority of our cases did not allow a microscopic diagnosis of malignancy from cytologic studies.

Invasion of blood vessels without invasion of capsule was not encountered in our cases. Invasion of the capsule alone was found in 32 adenomas, while both phenomena were present in 14 cases. The adjacent thyroid tissue proper was invaded by tumor cells in 12 cases and adjacent neck structures (muscle) in 1 other case. No case showed distant metastases at the time of operation. Cervical nodes, lungs, and bone were free of cancerous growth as far as clinical examination, including x-ray, could determine.

Follow-up studies. The time of observation after operation in our cases varied between 12 years and 1 month. At present, of the 42 traced patients, 38 (90 per cent) are alive and without evidence of disease. Two patients are

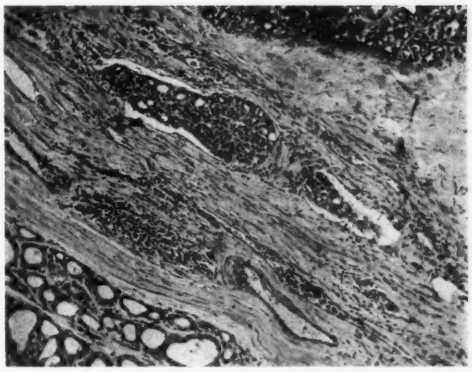

Fig. 5. Case. 8. Invasion of capsule and blood vessel of smallfollicular adenoma in 50 year old female (×72). Six years after bilateral thyroidectomy, the patient does not show evidence of recurrence or metastasis.

dead. One patient died 4 years after operation of cirrhosis of the liver and without evidence of thyroid disease, at the age of 58 years; the second died at age 67, two years after her goiter operation. She had a lobe removed which weighed 135 grams, and had multiple nodules 2 to 8 millimeters in size. In this case the atypia was of grade 1, and there was gross and microscopic invasion of the capsule but no blood vessel invasion. Twenty-one patients were living after 5 years or longer, 4 lived 10 years or more, and 39 lived longer than 2 years. According to Warren, recur-

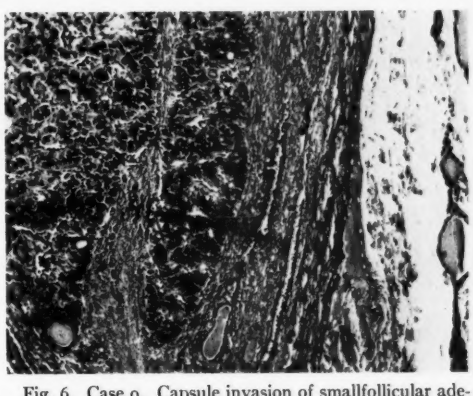

Fig. 6. Case 9. Capsule invasion of smallfollicular adenoma (×72) of 25 year old female who had noticed enlargement of the neck for 1 year. The patient is living and well 7 years after left lobectomy.

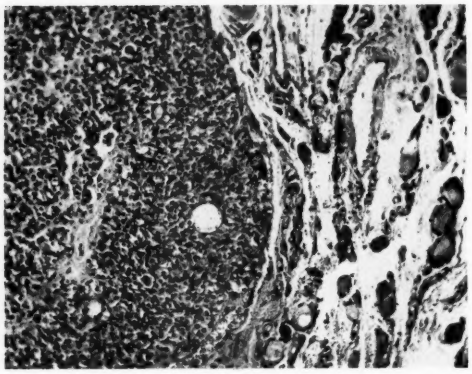

Fig. 7. Case 43. Multinodular goiter in 65 year old female. One grayish node (Fig. 2) showed microfollicular structure and invaded thyroid tissue proper (×72). The patient is living and well after bilateral thyroidectomy.

rence and death occur, as a rule, in the first year after operation for malignant goiter.

DISCUSSION

While Warren and Meissner, in their recent atlas on tumors of the thyroid, classify invasive adenoma as cancer, they believe that on account of their excellent prognosis these tumors should be distinguished from other types of cancer. In the clinic they prefer the term "adenoma with invasion," and they regard excision of the tumor with its capsule and a margin of adjacent thyroid tissue as adequate treatment.

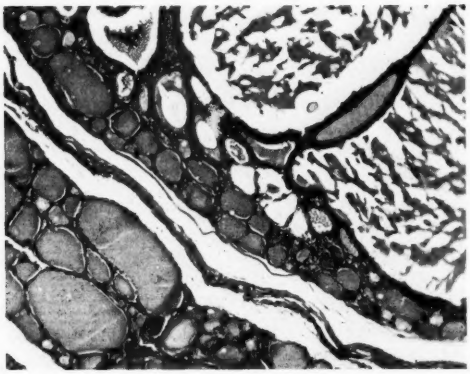

Fig. 8. Case 18. Large follicular adenoma of 67 year old female. The tumor invaded the thyroid tissue proper. The patient is living and well 3 years after lobectomy.

Postoperative irradiation or more radical surgery, such as neck dissection, are in their opinion not necessary for this type of tumor. The cure rate should be over 90 per cent with conservative surgery alone. Hare and Salzman reported on 49 cases of alveolar adenoma with invasion which were removed surgically. The average age of their patients, 6 males and 43 females, was 45.2 years. There was no evidence of recurrence in any of their cases. The authors, therefore, do not include these tumors among clinical cancer cases in spite of histologic signs of malignancy.

Zimmerman believes that if invasion by an excised nodular goiter is demonstrated microscopically, the surgeon is not obligated to subject such a patient to radical neck dissection. Pemberton regards removal of malignant adenomas with a good margin of safety as sufficient radical procedure, while Beahrs and Judd recommend total lobectomy for malignant adenomas. They complete the operation as a total lobectomy if after subtotal lobectomy an unsuspected carcinoma is reported by the pathologist. Lahey and Hare believe that radical dissections of the neck are indicated in all cases of carcinoma arising in discrete adenomas where the carcinoma has eroded the capsule of the adenoma and has involved the parenchyma of the thyroid on the affected side. Cerise, Randall, and Ochsner perform hemithyroidectomy with removal of the isthmus for thyroid carcinoma without local metastases. Crile Jr. found that all invasive adenomas which had not been operated upon previously were controlled by operation without roentgen therapy. The invasive adenomas have, in his experience, little or no tendency to metastasize to cervical nodes and require nothing more than a complete lobectomy.

In 1953, Hazard reported on 32 cases of angioinvasive adenoma, 8 per cent of his malignant goiters. All his cases but 1 were atypical in structure, and of the 22 patients traced 5 years or more, 68.2 per cent had recurrences or metastases, and 20 per cent were dead of tumor. It must be concluded that Hazard applies the term "angioinvasive adenomas" to tumors of high malignancy and does not follow the general usage of "adenoma

ith invasion." Hazard, as evident from his hotomicrographs, includes in his group of ngioinvasive adenoma, tumors generally assified as follicular and solid carcinoma; eir poor prognosis depends on their histolog- anaplasia and not on angioinvasion.

Recently, Crabtree and Hunter Jr. reported 31 patients with invasive adenomas among 5 cancer cases. Only 2 recurrences were bserved, and no patient died of thyroid dis- se. The authors recommend lobectomy if a litary node is present and subtotal thy- idectomy if the goiter is multinodular. No dditional therapy seems indicated for in- sive adenomas.

SUMMARY

1. During the last 10 years, 46 cases of in- sive adenoma of the thyroid were observed the Hertlzer Clinic, Halstead. This type tumor was encountered in 27.7 per cent of ll malignant goiters.

2. Forty-three of the invasive adenomas ere observed in females and 3 in males. The ges ranged from 18 to 73 years at the time of peration. The average age of the female pa- ient was 39.1 years.

3. Enlargement of the neck was noticed by hese patients for from 2 weeks to 52 years. A clinical diagnosis of exophthalmic goiter was made in 2 cases and of toxic nodular goiter in 1 case.

4. Bilateral subtotal thyroidectomy was performed on 17 patients, lobectomy in 29 patients. In no instance was radical neck dissection performed, neither was isotope therapy administered. Only 3 cases had postoperative x-ray treatment.

5. The weight of the surgical specimens varied between 11 and 318 grams. In 31 cases a solitary node was found, in 9 two nodes were present, and in 6 there were multiple nodules involving the whole lobe. Twelve adenomas were uniform in structure, most of them showing a microfollicular architecture. Twelve times a combination of trabeculae and smallest follicles was noted. Microscopic study did not reveal cytologic criteria of malignancy, and the tumors differed from benign adenomas only by their invasive tendency. Microscopic invasion of blood vessels alone was never encountered, invasion of the capsule alone in 32 adenomas, while both phenomena were present in 14 cases. The adjacent thyroid tissue proper was invaded by tumor cells in 12 cases, and surrounding neck structures in 1 case. None of our cases showed distant metastases at the time of operation.

6. Of our 42 traced patients, 38, or 90 per cent, are alive and without evidence of disease. Two patients are dead. One, at the age of 58 years, died 4 years after operation, of cirrhosis of the liver. The second, at age 67, died of her thyroid disease, 2 years after removal of an adenoma which showed gross invasion of the capsule but no angioinvasion. Twenty-one patients were living after 5 years or longer, 4 lived 10 years or more, 39 lived longer than 2 years.

CONCLUSIONS

Invasive adenoma of the thyroid occurs in about one-fourth of all malignant goiters. Grossly and microscopically these tumors are identical with benign adenomas except for microscopic invasion of blood vessels or of the capsule.

The prognosis of these tumors is excellent. They are as a rule curable by simple lobectomy. Radical neck dissection, x-ray, or isotope treatment is, in our experience, not indicated in this type of thyroid tumor.

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ASEPTIC NECROSIS OF THE FEMORAL HEAD IN DOGS

Effect of Drilling and Bone Grafting

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THE treatment of aseptic necrosis of the femoral head complicating intracapsular fractures of the femoral neck is one of the most serious problems confronting orthopedic and fracture surgeons. The many reported pathologic and roentgenologic studies of clinical and pathologic material clarify the pathology of ununited fractures of the neck of the femur with or without aseptic necrosis, but utilization of this knowledge, has not been made by the clinicians in the diagnosis and treatment.

The use of drilling and insertion of bone grafts in the treatment of ununited fractures of the femoral neck has long been practiced. Indeed, bone transplants have been used in the treatment of fresh intracapsular fractures of the neck of the femur.

Relatively recently Phemister obtained superior results following drilling and bone transplantation to aid in the transformation of a necrotic femoral head into a viable one. A modification of the method used by Compere and Lee in the treatment of ununited fractures of the femoral neck was employed.

The drilling removes some of the dead bone and allows ingrowth of blood vessels and callus from the neck into the remaining dead bone of the head. The rectangular grafts inserted to the articular cortex of the head act as strong struts to prevent collapse of the head during the period necessary for revascularization and increase of the frequency of union if an associated ununited fracture of the femoral neck is present. The method was considered useful in the treatment of cases in which refracture of the necrotic head and only slight displacement through the zone of creeping substitution have occurred. Examples of this type of collapse of the femoral head as the zone of replacement reaches the weight bearing portion of the acetabulum have been reported by Santos, Sherman and Phemister (also v.i. 6 week experiment dog 807).

The criteria for management of the necrotic femoral head with nonunion as set forth by Phemister will not be repeated here.

In an attempt to evaluate the procedure, experiments were performed in dogs. The purpose of this report is, first, to demonstrate the stages of revascularization which take place after drilling and insertion of bone grafts into a necrotic femoral head and, second, to determine whether such treatment results in a functional hip joint.

Experimental work toward producing aseptic necrosis of the femoral head has not been uniformly successful. Stewart was able to produce varying degrees of aseptic necrosis of the femoral head in rabbits and dogs by cutting the ligamentum teres and incising the periosteum of the neck. However, no regular sequence of events in the progression of the aseptic necrosis followed by transformation of the head could be demonstrated. Apparently, the vessels within the neck of the femur supplied enough blood to prevent complete necrosis.

Compere and Wallace studied the incidence in dogs of aseptic necrosis of the femoral head after transcervical fracture with or without accurate fixation. They found aseptic necrosis of the head in 2 of 6 dogs with accurate fixation, as compared to 9 of 12 dogs without any fixation of the fracture. Bony union occurred in all of the former and none of the latter. Although the incidence of aseptic necrosis was reduced by accurate fixation, it was not entirely eliminated. No attempt was made to show the course of aseptic necrosis since all of the dogs were sacrificed at 3 to 4 months. Furthermore, with accurate fixation of the fractures and union of the fracture, transformation of a partially necrotic head could occur

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TABLE I.—SUMMARY EXPERIMENTAL ASEPTIC NECROSIS FEMORAL HEAD IN DOGS

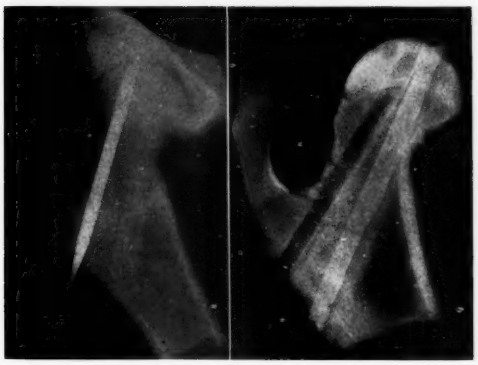
Dog No.	Operation	Duration, days	Union of osteotomy	Stage of transformation of head	Degenerative changes	Function
296	1 graft + 1 pin	21	Osseous	Very early along graft channel and margins of head	Very early, minimal clumping cartilage cells	Excellent hip motion
807	1 graft + 1 pin	45	Osseous, then refracture with nonunion	Collapse of weight bearing portion through zone of replacement	Minimal	Poor, did not bear weight
609	1 graft + 1 pin	56	Osseous	Vascular fibrous callus along either side of graft, 40 per cent of head replaced	Minimal, early fibrocartilage near graft and margins of head	Limp, pin protruded into acetabulum. Full range hip motion
505	1 pin + 1 graft	64	Osseous	60 per cent replaced. Ossification of fibrous callus along graft more extensive	Early	Excellent. No limp
477	2 grafts + 1 pin	85	Malunion, fragmentation	Fragments ⅓ replaced	Fibrocartilage over ends of fragments	Poor
423	Drilling + 2 pins	91	Union with dislocation of hip	70 per cent replaced. Ossifying vascular fibrous tissue in drill hole. Subchondral areas, partial necrosis	Minimal, marginal fibrocartilage	Limp, poor result, dislocation
533	Drilling + 2 pins	349	Union	Complete transformation hematopoietic marrow	Moderate	Good, 40 per cent restriction hip motion
539	1 graft + 1 pin	365	Union	Complete transformation hematopoietic marrow	Moderate	Normal function
189	1 graft + 1 pin	367	Union	Complete transformation hematopoietic marrow	Minimal	Excellent
424	2 grafts + 1 pin	361	Union	Deformed head	Severe eburnation	Limp, fair function
425	Drilling + 2 pins alone	371	Union	Almost complete, slight amount subchondral necrosis	Minimal to moderate	Good, bursa over end of pin

in 3 to 4 months in dogs, as will be shown in the experiments to be described.

PROCEDURE

Through an anterior approach the hip joint of adult mongrel dogs was dislocated by cutting the ligamentum teres. A 9/64 or 3/16 inch drill hole was made through the head and neck to the lateral subtrochanteric region. This was found to be easier than drilling from the lateral cortex to the head. The subcapital region of the neck was then osteotomized and all visceral capsular attachments were cut. The femoral head of the dogs in these experiments is considered to be necrotic after this procedure on the premise that "bone undergoes aseptic necrosis as the immediate result of injury or occlusion of the blood vessels in the absence of infection," as Phemister pointed out (3). As in bone transplants, the devascularized bone and marrow dies in the course of a few days, even though the osteocytes within the lacunae may not all disappear until 2 or 3 weeks have elapsed. Microscopic studies on femoral heads removed from patients as early as 15 days after neck fracture have shown evidence of aseptic necrosis.

Then the head was fixed with one or occasionally two ⅛ inch threaded steel wires. In 3 dogs, drilling alone was done. Two dogs operated upon early in the series had two tibial bone grafts inserted into drill holes. This was mechanically difficult so it was dropped in favor of a single tibial graft in the remaining animals. The animals were put in a single hip spica plaster dressing which was removed after 2 to 3 weeks. Penicillin was used postoperatively for 1 week or longer in all instances. Animals were sacrificed after a length of time varying from 3 weeks to 1 year. The hip joints were checked at intervals with roentgenograms. An attempt was made to obtain sagittal sections of all specimens removed at autopsy through the bone transplant and threaded wire sites with varying degrees of success. A total of 15 animals were used. Four infected animals are excluded. Table I summarizes the experiments and results.



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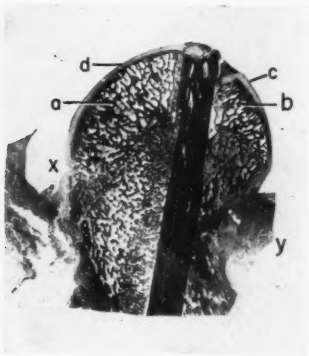

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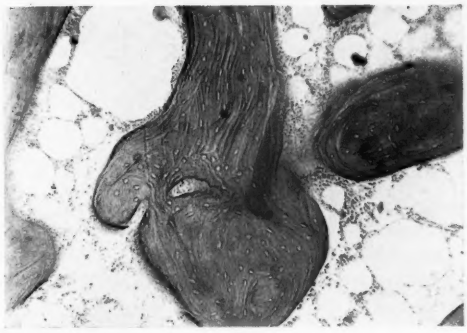

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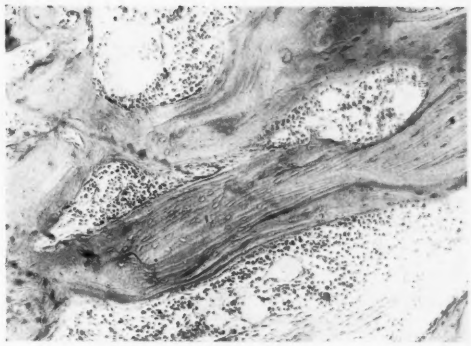

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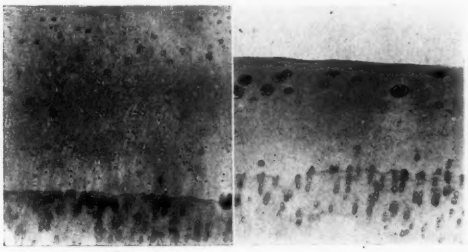

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Fig. 1. Three week experiment. a, Roentgenogram of specimen shows bony union of head and neck. b, Roentgenogram of the cut specimen demonstrates the pin tract, the bone graft, and indentations at the margin of the head and neck indicating the experimental fracture site. c, Microscopic section of the specimen through the graft site shows the united fracture (*x-y*) union of the graft to the head and neck and a zone of connective tissue marrow invasion above the osteotomy site. The letters mark the areas from which photomicrographs were taken. d, Necrotic bone and marrow without vascular invasion (*a* in Fig. 1c) is seen. e, Vascular marrow surrounds almost completely transformed trabeculae (*b* in Fig. 1c). Note creeping replacement of necrotic bone. f, Specimen showing little alteration of articular cartilage (*c* in Fig. 1c), ×60. g, Another area of articular cartilage showing clumping of cartilage cells and loss of staining power of cartilage cells (*d* in Fig. 1c). There has not been time for change in the subchondral bony cortex, ×60.

PROTOCOLS OF THE PERTINENT EXPERIMENTS

Three week experiment. One threaded pin and 1 graft were used. The plaster dressing was removed 2 weeks after operation. At 3 weeks the dog was bearing weight on the extremity. The dog was sacrificed at 3 weeks. Gross inspection of the hip joint showed the ligamentum teres firmly united to the acetabulum and femoral head. The articular cartilage of the head was smooth. The graft site was covered by fibrous tissue. The head and neck were united. Soft tissue was attached to the osteotomy site at the margin of the head. The cut specimen demonstrated a reddish zone half way into the head. The remainder appeared white. Roentgenograms of the

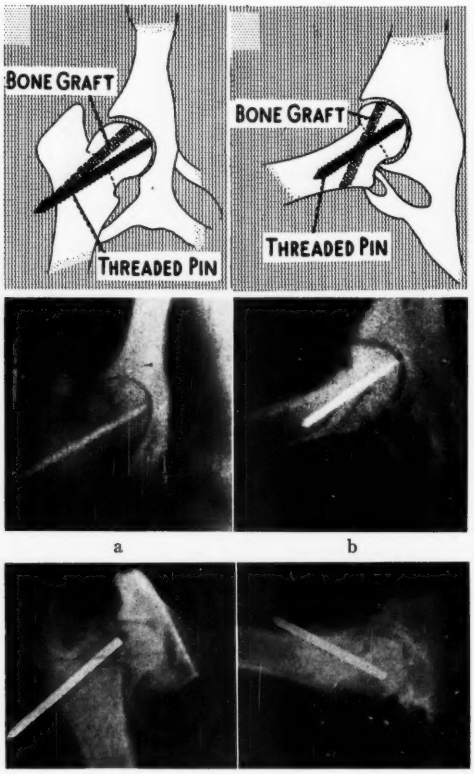

Fig. 2

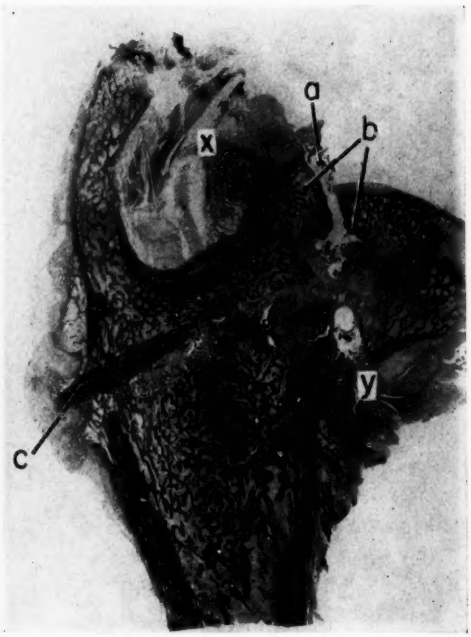

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Fig. 2

Fig. 2. Dog 807 (6 week experiment). a, b, Roentgenograms and artist's sketches at 3 weeks. Threaded pin in place. Head not displaced. c, d, Three weeks later. Pin has been extruded. Nonunion of head at margin of acetabulum is present. e, Line of surgical fracture with union of the head superiorly (*x*-*y*). Pathologic fracture, pseudoarthrosis, and collapse of the head at *a*, ×3. Note thin trabeculae and fibrous marrow at the margins of the pathologic fracture *b*, a portion of the transplant is seen united to lateral cortex of the femoral neck *c*.

Fig. 3. Eight week specimen showing lacunar absorption of dead bone and intramembranous ossification of vascular connective tissue. ×68.

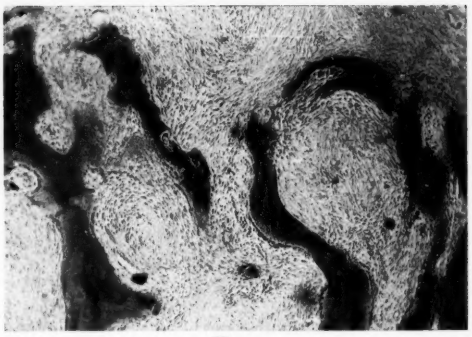


Fig. 3

whole (Fig. 1a) and cut specimen (Fig. 1b) show bony union of the femoral head and neck. The osteotomy site is visible at the margins. The density differences in the head and neck are not remarkable.

Microscopic section through the graft site (Fig. 1c) demonstrates the osteotomy site (*x*–*y*) and bony union between the graft, femoral head and neck above and below the osteotomy site. There is invasion by vascular connective itssue along the graft into the head and also from the margins of the head and neck where the capsule has reattached. Ossification of this tissue is present along the graft and in the marrow spaces. The invasion has progressed further along the graft channel

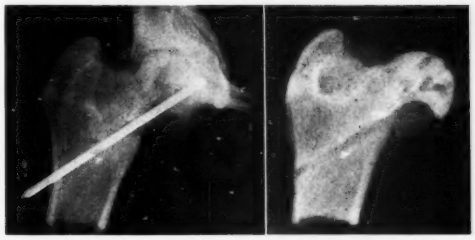
than it has at the periphery of the head. The upper three-fifths of the head has not been invaded by vascular connective tissue (Fig. 1d). An area near the advancing zone of invasion shows partial transformation of necrotic by living bone (Fig. 1e). The marrow is vascular. The articular cartilage appeared unaltered grossly and in some areas microscopically (Fig. 1f). In other areas (Fig. 1g) loss of staining power of the cartilage cells and clumping of cells indicate death of the cartilage and early degenerative changes.

Six week experiment (dog 807). Union of experimental fracture with pathologic fracture through zone of replacement and collapse of head.

Upon osteotomy of the neck a spike on the anteromedial side broke off with the head. After osteotomy of the neck, 1 tibial graft was inserted in the anterolateral aspect of the head and neck and 1 threaded pin in the posteromedial region. The 3 week roentgenograms show the pin in place (Fig. 2a, b). The film is of poor quality so that union of the surgical fracture could not be determined. At 6 weeks the dog did not bear weight on the extremity. Motion was limited in all directions and crepitation was audible and palpable. The pin was palpable far out of the lateral femoral cortex. Roentgenograms at this time (Fig. 2c, d) demonstrate the threaded pin extruded to the level of the osteotomy site. Collapse and nonunion of the head at the margin of the acetabulum have occurred.

Gross examination of the specimen showed nonunion of the head, fracture of the graft, and extrusion of the pin. There was a villous pannus over the head and transplant. The acetabular cartilage about the fovea was partly eroded.

Microscopic sections (Fig. 2e) reveal that the femoral head had united at the surgical fracture site (*x–y* Fig. 2e) but that pathologic fracture and collapse occurred when the zone of transformation reached the weight bearing area under the margin of the acetabulum (area *a* Fig. 2e). At the margin of the fracture site, bony trabeculae have been replaced for the most part by new bone and vascular fibrous tissue (area *b* Fig. 2e). Trabeculae are thinner there than in the subchondral region of the head or in the neck. The ununited head has been transformed partially along the pathologic fracture site, pin tract, and inferior margin of the head. A portion of the transplant is seen united to the lateral cortex of the femoral neck.



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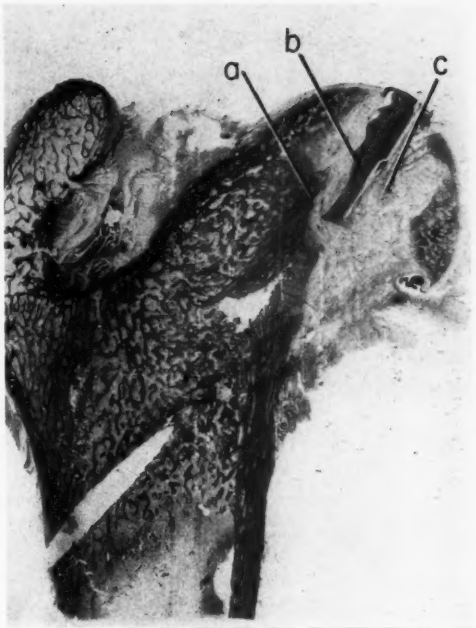
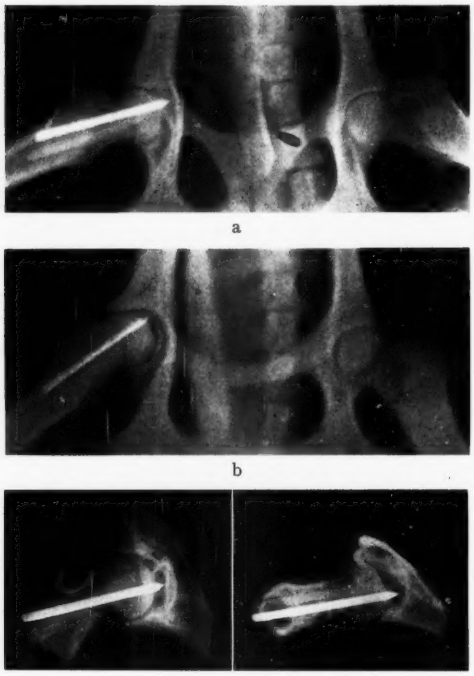


c

Fig. 4. Nine week experiment. a, Roentgenogram of specimen showing union in spite of poorly placed pin inferiorly in the neck. b, Roentgenogram of cut specimen demonstrates graft centrally in head surrounded by an area of reduced density. The pin tract is inferior. The superior quadrant of the head has not atrophied to the same extent as the neck and shaft of the femur. c, Microscopic section of the specimen shows the graft incorporated with neck (*a*), loose proximally and undergoing lacunar absorption (*b*); ossification of the fibrous marrow (*c*) has occurred.



a b c d

Fig. 5. Dog 189 (1 year experiment). a, There is bony union 3 weeks postoperatively. b, At 6 months. c, d, Specimen roentgenograms at 1 year showing normal appearance of femoral head except for slight downward tilting of the head and slight overgrowth of bone at the healed fracture site. The protruding pin has gouged the acetabulum.

Eight week experiment (dog 609). Bony union resulted from use of 1 graft and 1 threaded pin. Dog had a right hip limp. There was slight crepitation because of protrusion of the pin into the hip joint. The roentgenograms show areas of reduced density in the femoral head corresponding to regions of invasion and replacement of the head. This was most marked about the graft. One such area is demonstrated by a photomicrograph (Fig. 3). Intramembranous ossification of the vascular connective tissue and lacunar absorption of the dead bone is well illustrated in this specimen.

Nine week experiment (dog 505). In this animal, an excellent early functional result followed treatment of the avascular head of the femur with 1 tibial transplant and 1 threaded pin. Although the pin was out of the neck inferiorly (Fig. 4a) and the graft fractured within the head (Fig. 4b), both held long enough for union to occur.

Microscopic section (Fig. 4c) from the specimen revealed that the distal fragment of the graft united to the neck and underwent creeping replacement (area *a* Fig. 4c) while the proximal portion was loose and undergoing lacunar absorption (area *b* Fig. 4c). Extensive transformation of the necrotic bone has occurred. About the graft and along the pin tract in the head, there is much fibrous tissue in which ossification is occurring (area *c* Fig. 4c). The articular cartilage shows partial necrosis in many areas with early degenerative changes.

In an 85 day experiment (dog 477), treatment of the femoral head with 2 bone grafts and 1 threaded pin resulted in breakdown of the undrilled portions of the head. The malunited fragments of femoral head had been about a third replaced by living bone. Fibrocartilage had covered the fragments.

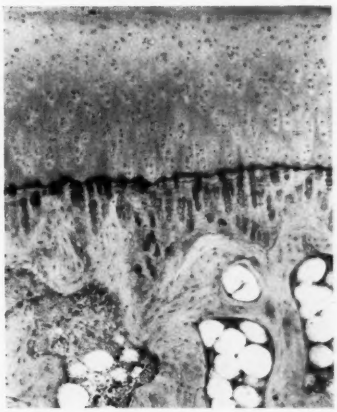
At the end of 1 year, severe degenerative arthritis with marked flattening of the femoral head of another dog (No. 424) treated by drilling and insertion of 2 bone transplants and 1 pin had occurred. In both of these experiments the grafts took up about one half of the total area of the head.

Three month experiment (dog 423). The dog's hip dislocated after treatment by drilling and insertion of 2 threaded pins. Union of the fracture and about 70 per cent substitution of the head by creeping replacement occurred in spite of the dislocation. The hyaline cartilage was partially replaced by fibrocartilage. The drill hole was filled by fibrous tissue in which membranous ossification occurred. There was no collapse of the head.

One year experiment (dog 189). This dog had an excellent functional result following the use of 1 tibial transplant and 1 threaded pin into the femoral head. The dog had walked without a limp. The hip moved freely at the time of sacrifice. Roentgenograms made at 3 weeks (Fig. 5a) and at 6 months (Fig. 5b) show union of the fracture in excellent position.

Gross examination of the specimen demonstrated solid bony union of the femoral head

e



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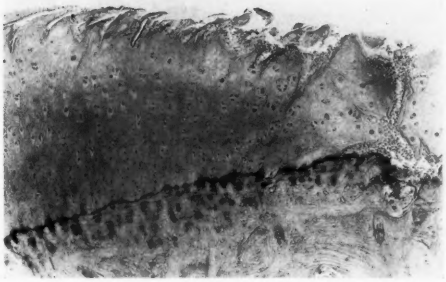

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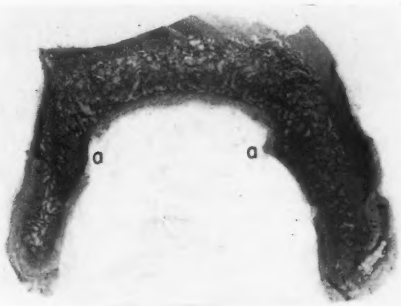

i

Fig. 5. e, Microscopic section of a sagittal slice of the specimen through the graft site shows the relatively normal revascularized head with union of the fracture site (×2) and almost completely revascularized transplant. f, Viable bone and cartilage from top of femoral head near bone graft (*a* in Fig. 5e). g, Fibrillation and faulting of cartilage from inferior portion of head (*b* in Fig. 5e). The subchondral cortex is incompletely replaced. Note vascular invasion at the fault in the cartilage. h, The bone transplant in the head is almost completely replaced by living bone (*c* in Fig. 5e). i, A microscopic section through the acetabulum showing the defect created by the protruding pin. Fibrocartilage covers the area (*a-a*).

and neck in normal position. The ligamentum teres was firmly reattached. The articular cartilage appeared to be in good condition. There was slight protrusion of the pin into the hip. This gouged an area of the acetabulum. A cartilaginous loose body was attached to the synovium.

Specimen roentgenograms (Fig. 5c, 5d) show a slight downward tilting of the head and overgrowth of bone superiorly at the healed fracture site. The cartilage shadow is of normal width in spite of the pin projecting into the acetabulum. The bone transplant is well incorporated as evidenced by its indis-

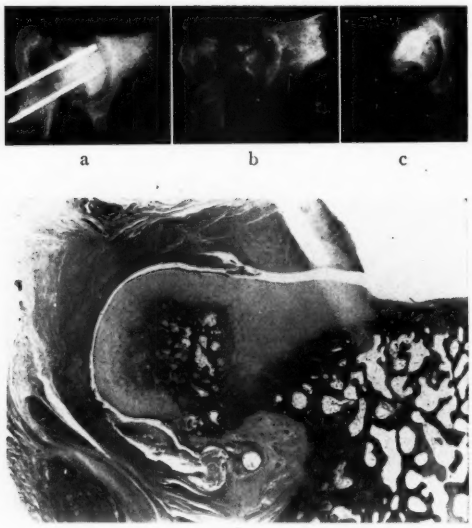

Fig. 6. a, b, c, Roentgenograms of the specimen showing moderately severe degenerative arthritis. Marginal lipping and osteocartilaginous loose bodies are evident. The cartilage shadow is of normal width, however. d, A low power photomicrograph from the superior margin of the head demonstrates a marginal osteophyte.

tinct outline. The microscopic section (Fig. 5e) through the junction of the graft and femoral head shows the head completely substituted and incorporation of the graft. Except for some areas of the subchondral cortex, living bone and hematopoietic marrow are present (Fig. 5f, area *a* Fig. 5e). The bulk of the articular cartilage is alive and does not appear to have undergone necrosis and replacement by new cartilage. Inferiorly, however, there is fibrillation and faulting of the cartilage with vascular invasion through the subchondral cortex (Fig. 5g, area *b* Fig. 5e). A higher power photomicrograph of the graft demonstrates almost complete substitution by living bone (Fig. 5h, area *c* in Fig. 5e). Fibrocartilage covers the defect in the acetabulum created by the protruding pin (Fig. 5i).

In another 1 year old experiment (dog 539), the dog had a moderately severe degenerative arthritis of the hip joint. Roentgenograms of the specimen before (Fig. 6a) and after (Fig. 6-b, 6c) splitting the specimen demonstrate marginal lipping and osteocartilaginous loose bodies but a relatively normal cartilage shadow. The superior pin projects into the joint. A photomicrograph of the superior marginal osteophyte is shown (Fig. 6d).

In specimens from the 2 remaining animals (dogs 533 and 425) which were followed for a year before sacrifice, the changes already described are present.

SUMMARY AND DISCUSSION

Four of 15 dogs became infected. Of 11 noninfected dogs, 8 developed union of the head and neck without complication. One dog's hip dislocated, but the fracture of the neck united in spite of this. In 1 animal, a 6 week experiment, early union at the osteotomy site did occur superiorly, but sometime after 3 weeks a pathologic fracture occurred through the head when the weak zone of creeping replacement reached the margin of the weight bearing portion of the head beneath the acetabulum. Malunion secondary to fragmentation of the femoral head occurred in another dog when an attempt was made to insert 2 bone transplants, and there was a poor functional result. Thus, in the 8 dogs without complication a satisfactory functional result was obtained.

The results of these experiments corroborate the findings of Compere and Wallace that accurate fixation of a femoral neck fracture in dogs will produce bony union. It cannot, however, be as definitely stated that accurate fixation will reduce the incidence of aseptic necrosis. In their experiments only partial necrosis probably occurred since the ligamentum teres was not cut. Furthermore, in those instances in which bony union followed accurate fixation, replacement of necrotic areas may have taken place before the animals were killed at 3 or 4 months as occurred in several of the animals described in this article.

The avascular femoral head of the dogs underwent creeping substitution in these experiments. In the earliest stages vascular osteogenic tissue was observed to invade most rapidly along the graft channel and at the margins of the head at its junction with the neck. Concomitantly, as the head united with the femoral neck, vascular connective tissue resembling fibrous callus invaded all

he intertrabecular spaces and gradually extended upward into the head. Further transformation of the head occurred from the region of the reattached ligamentum teres. Blood vessels were found in most of the marrow spaces at 50 to 60 days although only a half to two thirds of the necrotic bone was replaced. The subchondral cortex was slowest to undergo transformation. At 1 year replacement was complete except for occasional areas of dead bone in the subchondral cortex. Varying degrees of synovial hyperplasia and degenerative arthritis occurred. The degenerative changes appeared to be most marked in the hips of dogs where the pins used for fixation protruded from the head and gouged the acetabulum. In general, however, the articular cartilage did not undergo complete necrosis but appeared to survive from nutrition which was received from the synovial fluid as is the case in children.

Some of the most characteristic histologic features of the replacement of the necrotic femoral head were shown. These are similar to those described in humans.

CONCLUSIONS

The experiments present evidence that the healing of aseptic necrosis of the femoral head in dogs was aided by drilling particularly and insertion of a tibial bone graft. A high incidence of bony union without collapse was obtained in the presence of an avascular femoral head. Rapid invasion of the drill hole or graft channel by vascular osteogenic tissue in advance of similar invasion at the junction of head and neck is a significant factor in the rate of transformation. Satisfactory hip function was obtained in those animals without complication.

The results of these experiments strongly suggest, therefore, that treatment of the necrotic femoral head by drilling for revascularization and bone grafting to give support and aid in union of fragments is a biologically sound procedure.

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THE EFFECT OF POSITIVE AND NEGATIVE PRESSURE RESPIRATION ON UNILATERAL PULMONARY BLOOD FLOW IN THE OPEN CHEST

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RESPIRATORY acidosis develops in patients undergoing open thoracotomy surgery unless adequate ventilation is maintained. Gabbard and Stead and their associates have shown that manually assisted respiration may provide inadequate alveolar ventilation which results in respiratory acidosis. Gibbon has also pointed out that neither the Mautz nor the Crafoord (1) intermittent positive pressure respirators prevent carbon dioxide accumulation.

This apparent need for more adequate ventilation during open chest surgery stimulated us to investigate the possibility of adding a negative phase to an intermittent positive pressure respirator. Anesthetists have noted that satisfactory lung deflation is often difficult, especially in those cases with emphysema or other parenchymatous diseases which result in loss of elastic recoil. With the addition of a negative pressure phase more complete deflation and thereby more adequate ventilation may be accomplished and prevent carbon dioxide accumulation.

The experimental investigation of negative pressure led us into three phases of this problem. One was the study of the possible dangers and morphologic changes that take place with various degrees of negative intratracheal pressure. The second phase is a study of gas flow and ventilatory efficiency when positive and negative pressure respiration is used, and this portion of the study is in progress. The third phase is concerned with the effect of positive and negative pressure respiration upon circulation.

Watrous gives an excellent review of the many reports of investigators showing that positive pressure is detrimental to the circulation. On the other hand, however, other investigators have shown that the circulation was benefited by negative pressure deflation in the intact chest. With these observations in mind we were interested in studying the effect of negative pressure upon the circulation under conditions similar to those existing during open thoracotomy procedures and this report concerns itself with the results and conclusions from that study.

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APPARATUS AND METHODS

The experimental arrangement is shown diagrammatically in Figure 1. An unobstructed, intact airway was created in dogs anesthetized with intravenous nembutal by passing a No. 30 Magill intratracheal catheter and distending the distal balloon. The intratracheal tube was then attached by wide bore corrugated tubing to an anesthesia machine with a carbon dioxide absorber in the expiratory limb of a closed circuit. The anesthesial bag was enclosed in a plastic case similar to that used in Mautz's respirator. Pressure around this bag could be changed quickly from positive to negative or maintained at atmospheric by means of an apparatus specially designed and constructed for our use. This pressure changer operates on compressed air; the negative pressure is obtained by utilizing the Venturi principle. Needle valves could be adjusted to produce various degrees of positive and negative pressure and since the instrument was hand-operated, the duration of the various phases of the respiratory cycle could be changed as desired.

Intratracheal pressure was optically recorded by a Frank segment capsule connected by rubber tubing to a side arm of the adapter attached to the Magill catheter. Central

aortic and right atrial pressures were recorded through metal cannulas passed into these chambers via the left carotid and right external jugular vein, respectively. The cannulas in turn were connected by lead tubing to Grigg manometers with rubber membranes of adequate sensitivity and frequency.

The dog was turned slightly on the right side and the chest entered through the left fifth interspace. The left main pulmonary artery was isolated and incised so that the proximal and distal ends could be cannulated by short right angle sounds. These cannulas carried blood through an optically recording electromagnetic rotameter type of flow meter. The blood was made noncoagulable by the intravenous injection of heparin. A third Grigg manometer was connected by lead tubing to a side arm of the efferent limb of the rotameter to record the pressure of the blood perfusing the left lung.

It should be emphasized that insertion of the rotameter into the left pulmonary artery increases resistance to blood flow. Since blood may be shunted through the right lung which has a lower resistance the rotameter flow is not quantitatively valid. However, the rotameter flow is qualitatively indicative of the changes in pulmonary vascular resistance.

The light beam for each manometer was deflected from a fixed baseline by a known pressure at the end of a record. By shunting the blood around the rotameter it was possible to record zero flow at the beginning and end of each record without interrupting flow through the left lung. At the end of an experiment each manometer was statically calibrated over wide ranges of pressure and the flow meter with flows ranging from 50 to over 500 cubic centimeters per minute. The dog's blood was used for the flow meter calibration and the animal board was used as a reference level for all pressures. The vascular pressures were measured in millimeters of mercury and the endotracheal in centimeters of water. The data are taken from 6 experiments.

EXPERIMENTAL RESULTS

Effect of prolonged positive and negative pressure on unilateral pulmonary blood flow. Records in Figure 2 demonstrate the effect of prolonged positive and negative pressure on pulmonary blood flow. Figure 2a shows a marked fall in pulmonary (*BF*) flow (482 to 170 c.c./min.) as intratracheal pressure (*IP*) is gradually elevated to 33 centimeters of water over a 4.0 second period of time. Concomitant with this fall in flow, the perfusion pressure (*PP*) rises from 18 to 27 millimeters of mercury. It is evident that resistance $\left(R = \frac{P}{F}\right)$ to blood flow through the pulmonary vascular bed has been greatly increased by the application of positive intratracheal pressure. Aortic pressure initially rises with positive pressure inflation. This rise is thought to be due to the displacement of blood from the pulmonary veins toward the left atrium thereby temporarily increasing the left ventricular stroke volume. Three beats after pulmonary blood flow diminishes the aortic pressure falls in a parallel manner so that at the end of the positive phase the systolic pressure is only 130 millimeters of mercury as compared to the control value of 170 millimeters of mercury. After release of the positive pressure, the perfusion pressure returns to a control level and the pulmonary blood flow quickly rises and exceeds the control rate. This apparent overflow occurs as a result of the sudden decrease in resistance to pulmonary blood flow and the forward propulsion of the excess blood that had been backed up in the right venoatrial ventricular system. Again, after a 3 beat delay, the aortic pulse reflects this rise in blood flow by an increase in pulse and systolic

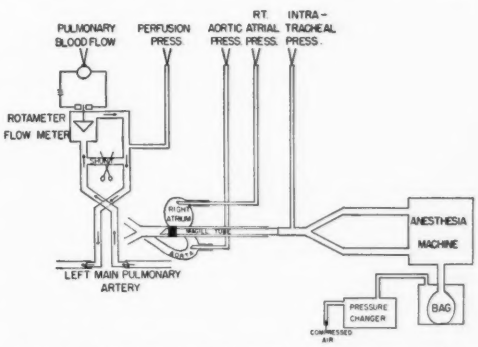
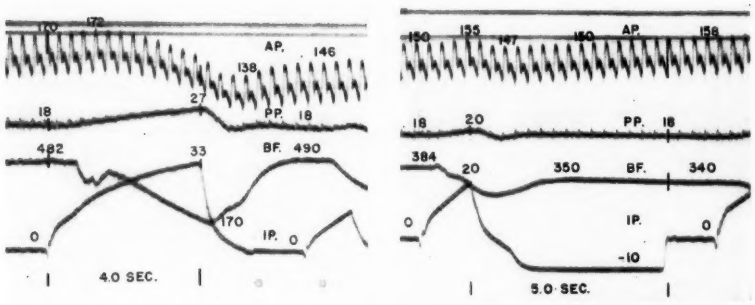


Fig. 1. Diagrammatic illustration of experimental arrangement.



a b

Fig. 2. a, The effect of prolonged positive intratracheal pressure on pulmonary circulation. b, The effect of prolonged negative intratracheal pressure on pulmonary blood flow. *AP*, Aortic pressure; *PP*, perfusion pressure; *BF*, pulmonary blood flow; *IP*, intratracheal pressure; *M*, mean pulmonary blood flow.

pressures. In several similar experiments it has been observed that as long as 5 minutes elapse before complete circulatory recovery occurs after a period of positive pressure.

Figure 2b shows the effect of sustained negative pressure on pulmonary circulation. The flow remains steady after the initial fall due to the positive phase. Even when the intratracheal pressure is abruptly returned to atmospheric, there is no change in pulmonary flow. The perfusion pressure is not affected by the negative intrapulmonary pressure. The 10 cubic centimeter per minute decline in flow (350 to 340 c.c./min.) during this extended expiratory phase occurs without negative pressure and probably represents a gradual readjustment of the circulation to a mean flow not influenced by intermittent lung inflation and deflation. The aortic pressure reflects the changes brought about by the positive pressure lung inflation, but then it gradually rises so that within 7 beats the control level (150 mm. Hg) is reached, followed by a continued rise. This shows that 7 to 9 beats are required for return of the aortic pressure to a control value and further recovery occurs if the expiratory phase is prolonged before circulation is again interrupted by positive pressure inflation. As will be seen in later experiments this time necessary for recovery is of great importance in determining the pressure profile which will interfere least with circulation.

Pulmonary blood flow with positive and negative pressure respiration. Figure 3 shows segments taken from the same continuous record that depict the effect of combining positive and negative pressure on circulation during a respiratory cycle. The addition of a negative phase (Fig. 3b) did not change the mean blood flow (394 versus 394 c.c./min.) when compared with a respiratory cycle with positive pressure alone (Fig. 3a). The differences between these two records are the result of the higher (24 versus 19 cm. H^2O) intratracheal pressure for a longer duration (1.6 versus 1.4 sec.) in segment shown in Figure 3a.

Additional evidence that negative pressure does not affect pulmonary vascular resistance in the open chest is shown in Figure 3c. These two successive cycles with identical positive pressure phases demonstrate that even if the negative pressure is changed from $-.2$ to -4 centimeters of water mean flow remains exactly the same and the flow curves may be superimposed, as are the right atrial, aortic, and perfusion pressure tracings.

In these experiments, simultaneously recorded right atrial pressure shows a definite rise with elevation of intratracheal pressure. For purposes of accuracy and analysis the atrial curves are measured at two points, namely, the Z and V points. The Z point (digits below the atrial tracing) is the atrial pressure immediately before isometric ventricular contraction when there is a common atrioventricular cavity. This pressure reflects the end diastolic right ventricular pressure. The V point (digits above the atrial tracing)

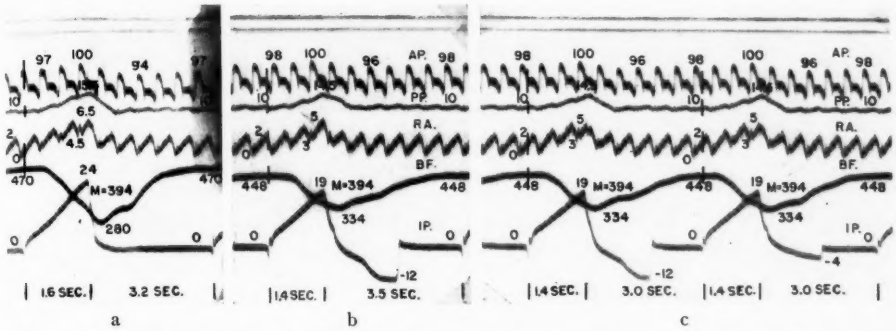


Fig. 3. Records showing effect of combined positive and negative respiration on pulmonary circulation. *AP*, Aortic pressure; *PP*, perfusion pressure; *RA*, right atrial pressure; *BF*, pulmonary blood flow; *IP*, intratracheal pressure; *M*, mean pulmonary blood flow.

is the atrial pressure prior to the opening of the A-V valves and is the pressure measurement most free from ventricular influence. Since the Z and V point pressures rise in a parallel fashion and the pressure goes up slightly before or concomitant with the perfusion pressure, it must be concluded that this rise in right atrial pressure is due to external compression of the right atrium and possibly to change in hydrostatic level, as the lungs are inflated. If this rise were due to a back pressure effect, one would expect the perfusion pressure to rise at least 1 beat before the atrial, and the Z point (i.e., right ventricular end diastolic pressure) more than the V point. During open chest surgery, as in these experiments, with the patient in a lateral decubitus position, it is reasonable to assume that compression of the afferent structures occurs with lung inflation and shift of the mediastinum.

Importance of the duration of positive phase. Analysis of various records from this study reveals that mean left pulmonary blood flow depends more upon the duration than the height of the positive pressure. Figure 4 demonstrates this observation. Figure 4a shows the effect of a 25 centimeters of water positive pressure phase occupying 2.0 seconds or 46 per cent of the cycle. The initial peak flow of 322 cubic centimeters per minute falls 198 cubic centimeters to a low of 124 cubic centimeters per minute and then returns to the original rate for a mean flow of 240 cubic centimeters per minute. In Figure 4b the same amount of positive pressure occupying only 32 per cent of the cycle (1.6 sec.) results in a smaller decrease in flow (116 vs. 198 c.c./min.) and a higher mean flow than observed in Figure 4a. The higher aortic pressure in Figure 4b reflects this greater flow. Comparison of Figure 4c, d and 4e, f shows similar changes for 18 and 12 centimeters of water intratracheal pressure respectively.

It is apparent that, if the positive pressure phase occupies one-third of the cycle, the mean flow remains constant over wide ranges of pressure. If the inspiratory and expiratory phases are about equal, however, the mean flow is diminished, aortic pressure falls and the degree of positive pressure becomes an important factor in determining the mean pulmonary flow.

DISCUSSION AND CONCLUSION

The continuous, simultaneous recording of left pulmonary artery blood flow, intratracheal, aortic, perfusion, and right atrial pressures make possible a study of the effect of positive and negative pressure respiration upon the circulation in the open chest. Heretofore, the mechanism for the depression of the circulation by positive pressure lung inflation has not been clearly defined in the open chest. There are two hemodynamic changes that account for this detrimental effect of positive pressure. One is a rise in right atrial pressure with a reduction in the venoatrial gradient and fall in venous inflow as has been

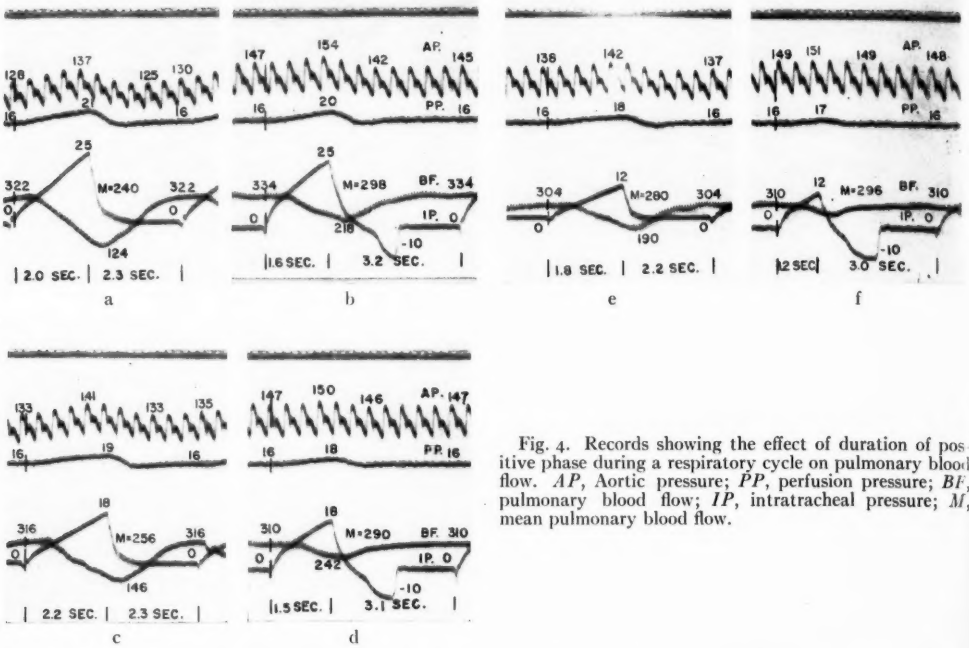


Fig. 4. Records showing the effect of duration of positive phase during a respiratory cycle on pulmonary blood flow. *AP*, Aortic pressure; *PP*, perfusion pressure; *BF*, pulmonary blood flow; *IP*, intratracheal pressure; *M*, mean pulmonary blood flow.

shown by Brecher. The other is an increase in resistance to blood flow through the pulmonary vascular bed, as has been shown by Edwards. Humphreys and associates (8, 9) concluded that the circulatory effect of positive pressure in the open chest was due primarily to reduction in venous inflow and that increased pulmonary vascular resistance played only a minor role.

If this were true, a reduction in right ventricular output (pulmonary blood flow) due primarily to reduced venous return would result in either no change or a fall in pulmonary arterial pressure. However, our experiments demonstrate that there is a rise in perfusion pressure which occurs at the same time as the right ventricular output diminishes. This indicates that there is a marked increase in pulmonary vascular resistance and that this increased resistance plays a major role in the detrimental circulatory effect of positive pressure lung inflation. It could not be determined how much the distortion of the right atrium reduced right ventricular output since venoatrial pressure gradient and vena caval inflow were not measured. It is apparent, however, that the reduction was not great enough to prevent the rise in perfusion pressure.

This increase in resistance to flow through the pulmonary vascular bed is supposedly due to compression of pulmonary vessels by the increased pressure in the lung parenchyma. A factor that may also play a part in contributing to increased resistance between the right and left heart is the rise of left atrial pressure which by its back effect could cause the same type of flow reduction and perfusion pressure rise. We were interested to find out if, by exposing the alveoli to negative pressure and thereby decreasing the pressure in the lung parenchyma, there would be vascular dilation and/or opening up of new channels so that resistance to blood flow would diminish. Thus, it was hoped that negative pressure in the open chest would offset the detrimental effect of positive pressure lung inflation on the circulation. These experiments, however, show that negative pressure deflation of the

lung has no effect upon pulmonary vascular resistance and the circulation is not affected. In the closed thorax, on the other hand, negative pressure increases cardiac output. The reason for this difference between the open and closed chest is quite evident, for in the intact thorax negative intrapulmonary pressure is transmitted to the intrathoracic afferent vessels and thereby increases venous return to the heart by enhancing the aspiration action of the thorax. In the open chest, however, negative intrapulmonary pressure neither increases venous return by lowering the afferent venous pressure, nor does it reduce pulmonary vascular resistance. Therefore, the circulation is not enhanced by negative pressure.

The experiments herein reported confirm the observation of Cournand and associates that the cardiac output depends more upon the type of pressure profile of a positive pressure respirator than it does upon the overall mean pressure. As described by those workers the positive pressure should be developed gradually and then abruptly dropped to atmospheric during the expiratory phase. Since positive pressure lung inflation decreases right ventricular output, the expiratory phase should be long enough to allow for compensation of this deficit. In the intact chest, Cournand found that cardiac output when indirectly measured was not decreased with intermittent positive pressure respiration provided that the expiratory phase was slightly longer than the inspiratory phase. From the open chest experiments we performed, it appears that the positive phase should occupy approximately one-third of the cycle and expiration, at atmospheric pressure, the remainder. This type of pressure profile allows for adequate recovery during expiration so that pulmonary blood flow remains constant even over wide ranges of intrapulmonary pressures.

The clinical importance of the detrimental effect of positive pressure during open thoracotomy procedures is obvious, but will not suffer from overemphasis. For example, anesthetists often apply sustained positive pressure to aerate atelectatic areas. As can be seen in Figure 2, such a period of sustained pressure has a profound effect upon the circulation and, therefore, should be avoided. Increased positive pressure applied intermittently as described herein will successfully aerate areas of collapsed lung without interfering with cardiac output. Wilhelm has shown that a distended anesthesia bag creates significant intrapulmonary pressure and, therefore, sustained positive pressure developed in this way should be avoided in order not to interfere with the circulation. It has also been observed by Carr and Essex that positive pressure is especially detrimental to the circulation when hypovolemia is present and therefore during such states great care must be used in applying positive pressure respiration. During open thoracotomy procedures as shown by Papper, one must keep in mind that increased intrapulmonary pressure can produce hypotension.

SUMMARY

1. In the open chest, positive pressure lung inflation interferes with circulation. This depression of the circulation under the conditions of this experiment is due primarily to increased pulmonary vascular resistance.

2. Negative pressure lung deflation does not augment the circulation in the open chest as has been observed in the intact chest.

3. The pressure profile which least interferes with circulation should be one-third positive pressure with an abrupt fall to atmospheric pressure for the remaining two-thirds of the respiratory cycle.

4. Attention is called to the clinical importance of a pulmonary blood flow reduction by positive pressure lung inflation.

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IN SUPPORT OF SURGICAL REMOVAL OF SMALL ULCERATING LESIONS OF THE STOMACH WITHOUT BENEFIT OF MEDICAL TREATMENT

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IMPROVEMENTS in preoperative preparation and surgical techniques—including anesthesia and the ability to minimize postoperative complications—have enabled surgeons to extend operative indications in many conditions, frequently quite beyond the horizon for which they are given credit by their medical colleagues and their more conservative fellow surgeons. No better example of this change in attitude can be found than in the indications for operating upon small ulcerating lesions of the stomach, thought to be benign from all clinical methods of investigation now at our command.

RESULTS OF MEDICAL TREATMENT

Long time observation of large series of individuals suffering from gastric ulcer is bringing to light the fact that medical treatment of such lesions is, on the whole, unsatisfactory and is attended by grave potential dangers: obstruction, hemorrhage, perforation, and, most serious of all, the ever present possibility of associated cancer. In a recent 5 year or longer follow-up of 414 small ulcerating lesions of the stomach reported from the Mayo Clinic (4), it was found that medical treatment had been disappointing. Relief of symptoms was satisfactory in only 20.5 per cent of cases. Cancer was present or developed in 10.4 per cent of the total group, and ultimate medical management was abandoned for surgical treatment in 33.8 per cent of cases. Cancer developed in approximately 5 per cent of the patients who had not undergone operation and were living at the end of 5 years. How many more of these patients could have been restored to health and happiness even greater usefulness to the community by gastric resection is problematic, but one has every reason to believe that the number is considerable. While this series of conservatively treated individuals undoubtedly did not universally receive the type of treatment best calculated to result in healing of their ulcers—because of their wide geographic distribution, which necessarily placed them under various types of medical management, or undoubtedly in some instances none at all—it no doubt represents the average type of medical treatment received by the rank and file of individuals suffering from such lesions in the past and the forseeable future.

Martin and Lewis, of Cambridge, England, were able to find very few long term follow-ups of cases of medically treated peptic ulcer. Of 96 verified gastric ulcers, 56 per cent had been under medical treatment for 10 years or longer, and were still active. They found that the longer medically treated ulcers are followed, the worse the results become. Natvig and associates, in a 3 year follow-up of 152 gastric ulcers, found 44 per cent symptom-free; 6½ to 9½ years later, the same cases were again reviewed by Qvigstad and Römcke, and the percentage had then dropped to 22. Malmros and Hiertonn followed 192 gastric ulcers treated medically for 7 to 10 years and found that 36.5 per cent showed favorable results, but not all of these patients were free of symptoms.

Martin and Lewis conclude from their studies that "To be perfectly honest, the post-investigation presented here is proof that medicinal ulcer therapy in the accepted form has resulted in almost complete failure. Yet it is remarkable that the very ability of medical treatment to stay the progress of an ulcer does not seem to have been previously questioned. The reason surely must be that short term results have been too readily accepted, probably for fear of surgery, and that cases have not been reviewed after a suf-

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ficient long interval. It is undeniable that medical treatment relieves the discomfort of most relapses but from present evidence, we cannot believe that it is any protection against further trouble if this is destined by the ulcer." And finally they remark that "the pathetic gratitude of patients at long last relieved by surgery emphasizes the burden of human misery which may have to be borne during the prolonged medical treatment of a chronic peptic ulcer." Banks and Zetzel followed 48 medically treated gastric ulcers which they believed received the usual type of medical supervision. Four had been followed more than 15 years; 7 for 10 to 15 years; 20 for 5 to 10 years; and the remainder for an average of 2½ years. Of the 48 patients, only 11 remained free of ulcer symptoms throughout the follow-up period, and 8, or 16⅔ per cent, of the 48 have died of verified carcinoma of the stomach.

In this relation, if one does rely upon "conservative" therapy, it is important to recognize the fact that any medical treatment necessitating long continued use is frequently abandoned by the patient. It is even more important to take into consideration the fact that an individual once relieved of symptoms by medical measures is prone to return to that method of therapy for a considerable trial period rather than to return to his physician for adequate investigation to determine why his symptoms recurred. These observations are pertinent to this discussion because there is widespread feeling that all seemingly benign ulcerating lesions of the stomach should be given a period of medical treatment in the well founded belief that the vast majority of such ulcers will respond favorably, at least temporarily. That such an approach to this problem is beset with grave dangers and is unwise in the vast majority of instances is easy to prove if one takes the time and makes the effort to review the data that have been accumulated.

It has been my privilege for many years to live in Hawaii, where the population is approximately 40 per cent Japanese. From studies of operative records, 840 being available from our clinic, which include operations for duodenal ulcer, gastric ulcer, and gastric carcinoma, it has been found that carcinoma of the stomach occurs in Japanese approximately 2 to 2½ times as frequently as it occurs in Caucasians and most other races. This same incidence of gastric cancer was also found in Board of Health statistics during a recent 5 year study of the causes of death. For this reason, the dangers and disasters of treating ulcers of the stomach medically have been frequently brought to our attention, more frequently no doubt than it has been to those caring for individuals with such lesions in the mainland United States.

HAZARDS OF MEDICAL TREATMENT

The factors that make medical treatment of all ulcerating lesions of the stomach a hazardous experiment and frequently a distressing one to physician and patient alike are in their sequence of importance: (1) the ever-present possibility of the lesion being or becoming malignant; (2) the possibility of perforation; (3) the possibility of hemorrhage; and (4) intractability of the ulcer resulting in varying degrees of invalidism of the patient.

Possibility of early cancer. What are the methods at the present time at our disposal that lead us to suspect the presence or absence of cancer in any given ulcer of the stomach? How dependable are these findings? What are the advantages and disadvantages of medical versus surgical treatment of such ulcers? And in this discussion in particular, what would have been the advantages of immediate operation upon small ulcerating lesions thought to be benign that later proved to be malignant by operation, after a period of medical treatment of a few weeks, or frequently, of months, or years of medical supervision or no supervision at all?

History. To approach this problem in an orderly and sequential manner, one must of necessity begin with the individual's history. There is nothing in an individual's history that will lend any great supporting evidence reliable in differentiating between a benign and a malignant lesion, such as is being discussed. It has been frequently stated that a long history of epigastric distress and other symptoms indicative of gastric disease suggests a benign lesion, and that a short history of a similar

nature, particularly in the older age group, uggests a malignant lesion. No doubt, this s of some significance, but certainly not sufcient to be of much clinical importance. ancer of the stomach, as is well known, is y no means limited to the older age group. hough it is less frequent in younger individals, we have seen a number of such lesions patients in their early 20's, and I believe e percentage of malignancy in gastric ulcers fully as high in the younger age group as it in the more elderly. We have found that in proximately 30 per cent of 300 gastric cers proved by surgery there was a history symptoms of 1 or frequently many years' ation, compatible with the diagnosis of a posedly benign gastric lesion. Horwitz es that 40 to 50 per cent of surgically and ological verified gastric cancers have an cedent history typical or strongly sugive of a benign ulcer.

hysical findings that suggest a malignant n are not of particular interest in this ussion, for if any are present, they indi- an advanced lesion which to all intents a purposes places the patient in a category which little can be expected regardless of t method of therapy used. Our only objecti in this presentation is to stimulate interest i he surgical removal of such lesions at a ti e when such treatment offers hope of cure o at least a considerable period of freedom fr recurrence.

he history and physical examination then being of such little help, in fact almost none at all, in differentiating benign from malignant lesions such as we are discussing, we must next turn to laboratory studies. These consist of, in diminishing order of relative importance: (1) x-ray and fluoroscopic examination of the stomach; (2) gastroscopic examination; (3) examination of the morphology of cells arising in the gastric wall; (4) gastric analysis; and (5) examination of stools for blood.

X-ray examination. The diagnosis of an ulcer by x-ray examination depends upon the demonstration of a niche. Other findings may be suggestive but are not diagnostic. To suggest benignancy, the ulcer should be small, since ulcer craters larger than 2.5 to 3 centimeters in diameter are recognized to be more frequently associated with malignancy. The crater should be smooth and punched out. The area around the ulcer is usually tender on palpation, and it is usually associated with pylorospasm and increased peristalsis, and surrounding rugae are normal or hypertrophic. Such ulcer craters penetrate the gastric wall more frequently than do malignant ones, and an associated pocket of contrast medium may be seen outside the gastric wall when this structure has been perforated. In contrast to these findings, a malignant ulcer is credited with having the following characteristics: the crater is more uneven in outline; and, due to piling up of malignant cells and infiltration surrounding the ulcer, the halo or meniscus sign of Carman, though rarely demonstrable, is considered to be a pathognomonic sign of malignancy. Tenderness is absent or less marked over the ulcer, and pylorospasm and hyperperistalsis are less evident. Infiltration by malignant cells of the tissues around the ulcer causes disappearance or atrophy of surrounding rugae and prevents or inhibits the passage of peristaltic waves through the involved area. Again, ulcers larger than 3 centimeters in diameter are often malignant. The location of the ulcer, whether along the greater curvature, in the fundus, in the prepyloric area, or on the anterior or posterior walls of the stomach, has been thought to be of significance, the danger of malignancy decreasing in frequency in the order mentioned. It has been repeatedly shown to our utter satisfaction and to that of many others that none of these signs either individually or collectively can give any reliable assurance that the ulcer is not malignant.

Gastroscopy. The value of gastroscopic examination, like that of x-ray investigation, depends upon the ability of the man who does it. Schindler recently stated that in a study of 273 gastric ulcers, an incorrect diagnosis had been made in 20 cases, or 7.3 per cent. Of 191 proved benign ulcers, 18 had been diagnosed by the gastroscopist as being malignant, and of 55 malignant ulcers, 2 were thought to be benign. In 14 cases, a sufficient study of the lesion could not be made to arrive at a definite conclusion. Gastroscopic

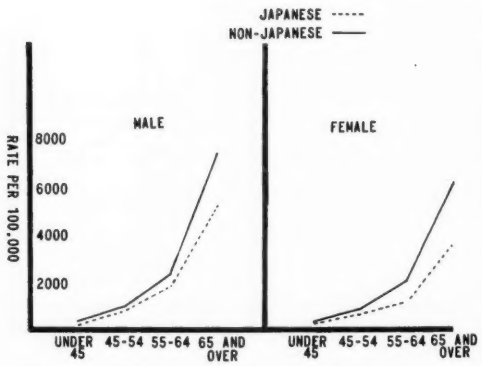

Fig. 1. Mortality rates in Hawaii from all causes comparing Japanese with non-Japanese. (From Rhea, T. R.: *Hawaii M. J.*, 1953, 13: 107.)

examination was either interpreted incorrectly or not at all in 12.4 per cent of the cases. Visualization of gastric lesions by gastroscopy, I am told, has limitations. The area just beyond the entrance of the esophagus along the lesser curvature, the area directly ahead of the gastroscope, lesions in the apex of the fundus, and an area just beyond the angulus of the lesser curvature may be impossible to visualize. At times, mucus, food particles, or bubbles of air obscure such lesions. The gastroscopic appearance denoting a benign ulcer has the following characteristics: (1) smallness of the ulcer; (2) regular punched-out appearance of its walls; (3) normal or hypertrophic appearance of the adjacent rugae with presence of small hemorrhages in the mucosa; (4) peristaltic waves passing through the involved area. Ulcers showing large size with irregular thickened edges that bleed easily, absent or atrophic surrounding rugae, and absence of peristaltic waves in the involved area are said to indicate malignancy.

Benedict states that he has been able by the use of the Benedict flexible operating gastroscope to secure biopsies of lesions of the stomach that have been of great value in differential diagnosis. When it is realized that the pathologist may find an area suspicious of cancer only after careful scrutiny of the removed specimen and only be able to prove the presence of malignancy on microscopic examination and at times only after examination of serial sections, it is difficult to see how the gastroscopist will be able with any degree of certainty to select the correct spot from which to secure a specimen for examination. It would seem that a wider use of this instrument by a greater number of gastroscopists would be necessary before determining the merits of this procedure.

Schindler states that it has been repeatedly observed that the gastroscopic examination of an ulcer is more reliable than examination of the gross specimen, since circulating blood gives the area a characteristic appearance. In this respect, it is a bit confusing to read in the July, 1953 issue of *Gastroenterology* these statements (first by Schindler and Desneux, page 329): "Signs of malignant ulcer were assumed to be—among other things—dark-red color of the ulcer wall." Then on page 355, Marshak and associates state: "On the other hand, in the carcinomatous ulcer, the thickened everted margin infiltrated with neoplastic tissue presents a yellowish appearance that is pathognomonic."

To say the least, the overall picture of the proper approach to the problems of gastric ulcer probably will not be appreciably altered by the gastroscope when so few patients are able to command the services of the few gastroscopists who are expert with this method of study.

Cytologic smears. The morphologic appearance of cells removed by gastroscopic washings and particularly specimens obtained by the use of the abrasive balloon have not in our limited experience been of help in differentiating between benign and malignant ulcers. Papanicolaou and associates (16) tested the gastric abrasive balloon in 154 cases. Of the 32 proved carcinomas, 30 were diagnosed correctly as malignant. There was 1 false positive. I dare say these carcinomas did not, for the most part, represent the very early lesions with which this discussion is concerned. In a more recent article by Cooper and Papanicolaou the following statement is made: "Very little is known regarding the value of this technique in the early diagnosis of gastric cancer because about two-thirds of the cases seen are inoperable and really small gastric cancers are a rarity. This proof will not be come by

easily or quickly but as the method becomes more widely known and generally used, it is felt that some cases of gastric cancer will be discovered in their earlier phases." Ochsner and Blalock state that although some of the newer diagnostic techniques, such as cytologic examinations of material obtained by the abrasive balloon suggested by Panico, Papanicolaou, and Cooper, may increase the incidence of positive diagnosis, until they have been proved to be of statistical value, it is imperative that lesions that are not cancer clinically be removed and that the patient be treated as if he had cancer.

In a recent communication, Dr. I. S. Ravdin, Professor of Surgery, University of Pennsylvania, has the following to say: "To my knowledge, there is no method of assurance that can tell the difference between a benign and a malignant gastric ulcer, at least at a stage when we can do something for the patient. I have not changed my ideas one bit, and I think as I look back upon the last three years, I am more strongly of the opinion than ever that gastric ulcers really ought to be operated upon." Another recent personal communication from Dr. Bentley Colcock, of the Lahey Clinic, was as follows: "We do very few abrasive balloon studies. It is very time-consuming and not nearly as dependable as a vaginal smear."

Rubin reporting on the present studies of exfoliative cytology, stated that the method is too complex for use as a general screening procedure. The fact remains that, despite the possibility of the future value of exfoliative cytology as regards lesions of the stomach, clinicians do not find at the present time that this method is of much practical clinical value.

Gastric analysis. Estimating the degree of gastric acidity with or without the use of histamine has not in our experience or in the experience of countless others been of great diagnostic assistance because too many ulcers proved malignant have had a normal gastric acidity. However, whenever an ulcerating lesion is found and no free hydrochloric acid is obtained after histamine, our suspicions that the ulcer is malignant are heightened.

Stool examination. The presence or absence of blood in the stools on a meat-free diet may

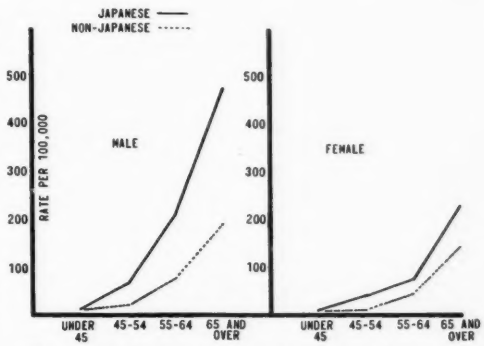

Fig. 2. Annual mortality rates for cancer of the stomach in Hawaii comparing Japanese with non-Japanese. (From Rhea, T. R.: *Hawaii M. J.*, 1953, 13: 107.)

be of importance in determining the presence of an ulcerating lesion of the stomach and of assistance in deciding whether or not such a lesion is responding to medical therapy, but it is of no help in differentiating between a benign or a malignant lesion.

Relationship of medical treatment to curability of gastric cancer. In our present state of knowledge, and with the diagnostic tools now at our disposal, it is conceded by practically everyone that there is no reliable method by which we are able to say whether or not any given ulcer is benign, or malignant, at a stage when surgery really has something to offer. From a practical viewpoint, then, the entire situation relative to the best treatment of questionable small ulcerating lesions of the stomach depends upon: (1) how many ulcers thought to be benign from all methods at our command prove to be malignant; (2) what percentage of benign ulcers ultimately become malignant, (3) what effect on ultimate cure does a period of medical treatment have; (4) what is the survival rate or cure of individuals with cancer in small ulcers operated upon immediately following diagnosis; (5) what is the operative mortality of gastric resection for these small lesions and the ultimate freedom of patients postoperatively of symptoms; and (6) how effective as regards immediate relief and permanent cure is medical treatment?

To take up these questions in sequence:

1. It is conceded, by those most competent to express an opinion, that 10 to 20 per cent of

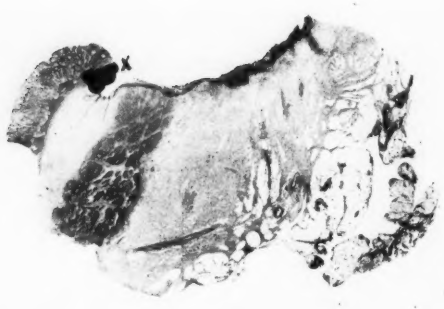

Fig. 3. An ulcer crater showing small area of malignancy at *X* emphasizing the difficulty of demonstrating malignancy in such an ulcer by any clinical method of examination.

gastric ulcers prove to be malignant after all methods of examination at our disposal indicate benignancy. A few of the figures in current literature are as follows: Lampert, Waugh, and Dockerty, in 550 resected ulcers thought preoperatively to be benign, found that 13 per cent were malignant. Allen found 14 per cent of patients treated as having benign ulcers proved to have cancer, many of these patients responding well temporarily to conservative therapy. Dr. Lahey in a recent article said, "Ideally I would like to resect every gastric ulcer if I could because in a series of 600 patients studied by Dr. Sara M. Jordan and Dr. Francis H. Smith in this clinic, 21 per cent of the ulcers proved to be malignant. Theoretically we should never treat a patient with gastric ulcer medically." With such statistics and the knowledge of other serious complications that so frequently arise, it is difficult to understand why Dr. Lahey and the Lahey Clinic in general have so consistently advocated a period of medical treatment for ulcers of the stomach. The same clinic advocating a period of conservatism for gastric ulcers insists on removing nodules in the thyroid without delay where the chance of malignancy is probably not more than 10 per cent and the dangers of other complications under observation alone are minimal in comparison. It is unfortunate that gastroenterologists are able in a large percentage of cases to bring about temporary clinical improvement in people with ulcers of the stomach because it lulls patients and physicians alike into a state of false security.

2. How many, if any, benign ulcers ultimately become malignant, no one can say. Such ulcers do not lend themselves to removal, serial sectioning for microscopic examination to determine their benignancy, then reimplantation for subsequent observation. In our own statistics, such an evaluation cannot be made because all ulcerating lesions of the stomach are considered to be malignant until proved benign by surgical removal. Pathologists have long debated the microscopic evidence which may suggest that a given cancer has been grafted onto a previously benign lesion.

Estimates in the literature range from 0 to 15 or more per cent, the determination being made on microscopic examination according to the criteria laid down by Warthin some 30 years ago, consisting of the following: (1) evidence of previous benign ulcer with characteristic induration and cicatricial fibrosis in the stomach wall with sclerosis of blood vessels; (2) greater part of the cicatrix free of neoplastic infiltration; (3) carcinoma in early stage of development limited to the borders or surface of the ulcer; and (4) the neoplasm infiltrating the ulcer scar to only a slight extent, so that there can be no doubt that the fibrosis is the result of the healing of an older ulcerative process and not secondary to the cancer.

The reliability of such evidence is problematic. One can only be sure that such a microscopic appearance is open to a wide range of interpretation. One can maintain that a great many of these ulcers ultimately do undergo malignant degeneration, which no one can disprove and be on as firm ground as those who maintain that this never occurs. It would seem strange if an organ so prone to cancer were not affected by such long continued chronic irritation. This is commonly cited as an etiologic factor for cancer occurring in most other parts of the body. Certainly many people with gastric cancer give a long history of epigastric distress compatible with a diagnosis of a benign gastric ulcer, and some have had an ulcer demonstrated in an area many years previous to the development of cancer in this

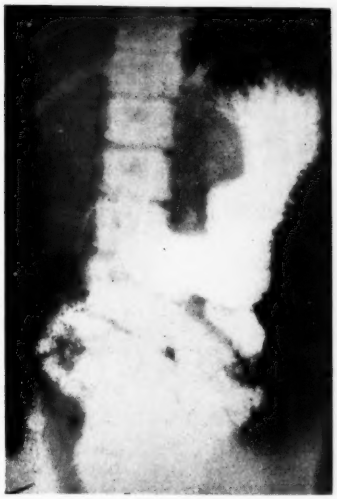

Fig. 4.

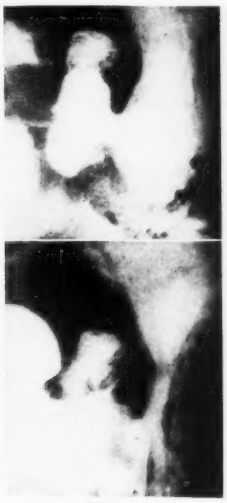

Fig. 5.

Fig. 4. Large benign ulcer, lesser curvature, thought to be malignant preoperatively.

Fig. 5. Small area of infiltrating cancer in gastric wall not demonstrable by x-ray examination, recognized by gastroscopy. Lymph node metastases.

particular area. Such circumstantial evidence, it would seem, would have some influence even on the most skeptical.

Early detection and immediate eradication has been the battle cry in all our attempts to head off the relentless advance of unchallenged cancer. There comes a day, an hour, even a second when surgical eradication passes from possible to impossible, and the cancer from a state of curability to a state of hopeless incurability, all dependent upon whether or not malignant cells have passed beyond the limits of surgical removal. We have been taught that to palpate or massage a malignant lesion is to invite its spread. If for this reason we should curtail the number and extent of examinations of breast lesions, how much more important must it be to remove malignant cells from the walls of the stomach, which are constantly undergoing massage from peristaltic activity! The frequent widespread metastases found at time of operation would seem to lend support to the belief that early dissemination is brought about by this means. Covert and Brindley and others reported over 50 per cent survival of patients for 5 years after gastric resection for carcinoma when no lymph node involvement was present, and this has been the experience of others writing on this subject. Certainly no one would disagree with the belief that the possibility of lymph node metastasis increases with the duration of the primary lesion.

4. The 5 year survival rate following gastric resection for malignant ulcers thought to be benign has been reported to be around 40 per cent. No doubt these figures are based on surgery done for the most part on ulcers failing to heal under a medical regimen. It would be interesting, enlightening, and probably encouraging to have a 5 or preferably a 10 year study on a large series of ulcers operated upon immediately following such a diagnosis, in which histologic examination showed the presence of cancer. It is this determination that would have the greatest influence on deciding whether or not a period of medical therapy is justified in this condition.

While I do not approve of any time spent on medical therapy for any ulcer of the stomach, for those who do, there are other factors having a practical bearing on the dangers of

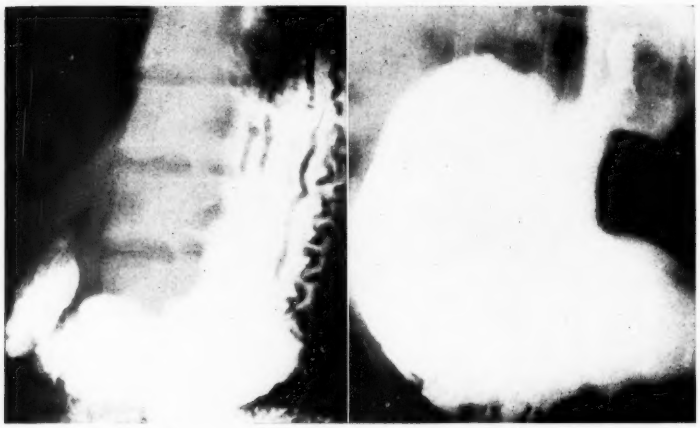

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Fig. 6. a, Ulcer of stomach in male, aged 41 years. Epigastric pain 3 years. Normal gastric analysis. X-ray evidence suggested benign lesion. Patient refused operation. b, Roentgenogram 5½ years later. Epigastric mass. Total anacidity. Exploratory laparotomy; lesion irremovable. Lymph nodes showed metastatic adenocarcinoma.

instituting medical therapy. Many people will not consent to hospitalization for treatment which they think can be conducted at home because of financial and other reasons. We have had the experience, and I am sure it has been the experience of many who believe in medical therapy, that many patients found to have small ulcerating lesions ultimately proved malignant are frequently symptomatically improved under medical treatment. X-ray and other studies may seem to corroborate this improvement. Such patients have later returned when examination left no doubt as to the diagnosis, and operation has revealed that nothing could be done; or, if resection or even total gastrectomy were done, they could be only palliative in nature.

5. What is the present surgical mortality of gastric resection for small ulcerating lesions, and what are the postoperative results? In most clinics familiar with the problems of gastric surgery, postoperative mortality is not over 1 or 2 per cent, and in many it is much lower. In our last 180 consecutive gastric resections for such lesions proved benign (and the same safety of operation applies to cases in which malignancy has been found only on microscopic examination), there has been 1 death. This death was due to postoperative evisceration, a technical error that should not have occurred.

It has been pointed out many times by Dr. Lahey and others that mortality and complications of surgery for duodenal ulcer are largely due to the difficulties of satisfactorily closing the duodenal stump. In resections for ulcers of the stomach, such complications are rarely encountered because the duodenum is not involved in the pathologic lesion.

One of the most frequent and serious complications following resection of the stomach for duodenal ulcer, and the one which vagotomy may help to prevent or cure, is stomal ulcer. While I have operated upon some 25 or 30 individuals for this complication, it has always been associated with duodenal ulcer, never with an ulcerating lesion of the stomach. I have inquired of many surgeons with extensive experience with gastric surgery about stomal ulcers associated with ulcers of the stomach, and few could recall having seen such a complication regardless of the type of surgery done for this condition. For this reason, it is neither necessary nor even advisable to remove the stomach as radically during resection for benign ulcer of this organ as is carried out when the stomach is being resected for duodenal ulcer.

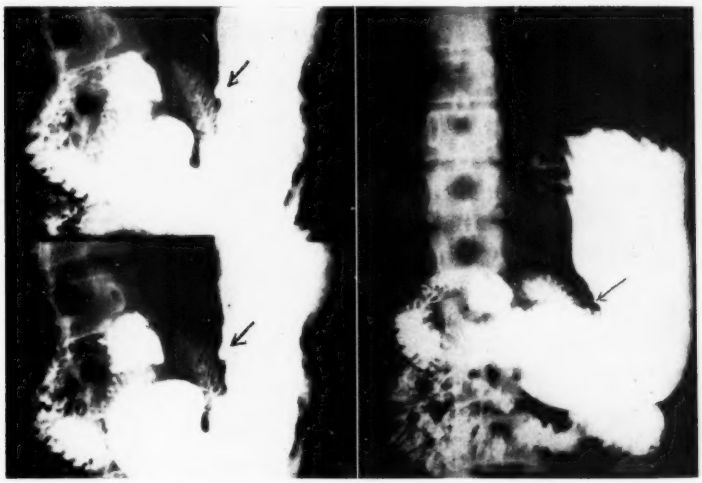

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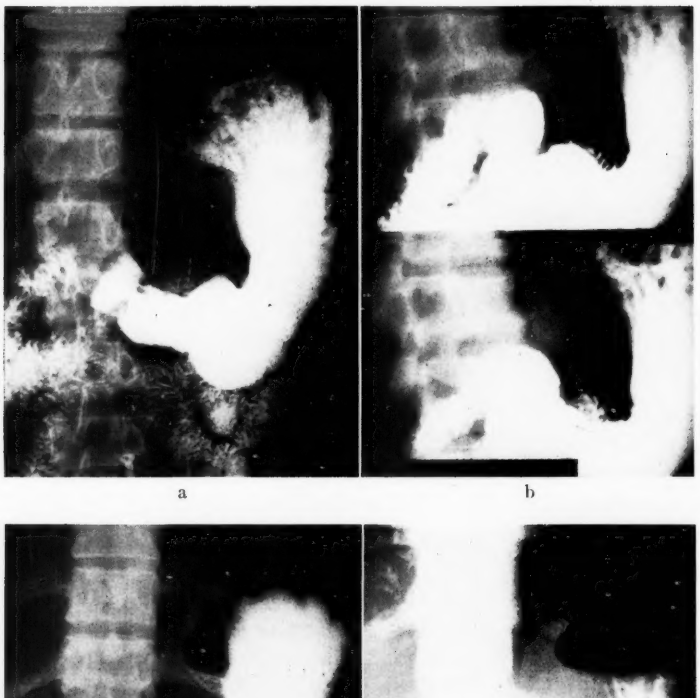
Fig. 7. Female, aged 35 years. Epigastric distress for several years. a, Small ulcer, lesser curvature. X-ray study suggested benignancy. Normal gastric analysis. b, After 3 weeks of medical treatment, patient felt better. X-ray study suggested improvement. Gastric resection 39 days after first x-ray study disclosed adenocarcinoma, grade IV.

These differences between the complications occurring following resection for duodenal and gastric ulcers are not universally appreciated by surgeons and are almost universally *not* appreciated by internists and gastroenterologists. A high percentage of good results following gastric resection for gastric ulcers is a fact recognized by everyone. Walters recently stated that 95 per cent excellent results were obtained in his hands, and Kiernan had only 1 unhappy patient following 162 gastric resections for gastric ulcer. Another complication of gastric resection which opponents of this operation tend to emphasize is the postgastrectomy or dumping syndrome. In properly executed resections, this condition occurs relatively infrequently and has not, with few exceptions, been a problem in our hands. Certainly, the unfavorable results following surgical removal of gastric ulcers do not approach the unfavorable and often very serious complications associated with such lesions that are left in place.

Complications of medically treated gastric ulcers. The evidence that has been cited up to this point would seem sufficient to establish the fact that there is no place for the medical treatment of ulcerating lesions of the stomach in patients who are good surgical risks and who can avail themselves of competent gastric surgery, and this type of surgery within recent years has become available to almost everyone. If there yet remain a few recalcitrant surgeons and a larger, but I feel sure, a diminishing number of gastroenterologists and internists yet to be convinced of the wisdom of this method of procedure, further evidence is readily available.

A considerable number of gastric ulcers give rise to serious hemorrhage, the treatment of which is both uncertain and attended by a considerable mortality, which is greater in gastric than in duodenal ulcers. A considerable number of gastric ulcers perforate and are admittedly best treated by surgical closure. Here, again, such catastrophes are not without appreciable mortality. Organic pyloric obstruction does at times occur secondary to gastric ulcers and not infrequently necessitates surgical intervention in patients who are correspondingly poor surgical risks. Needless to say, if these ulcers had been removed at an earlier and at a more opportune time, end results would have been correspondingly



a b c d

Fig. 8. Male, aged 28 years. Epigastric pain of several years' duration. a, Small ulcer, lesser curvature thought to be benign. b, Repeat x-ray film 1 week. Ulcer barely demonstrable. Advised repeat x-ray film 1 month. c, X-ray film 10 months later; no ulcer seen. Gastroscopic examination showed small superficial linear ulcer, lesser curvature. Operation advised; refused. d, X-ray film 3 years after first examination. Ulcer again demonstrated. Symptoms of epigastric pain and distress. Gastric resection 10 years after onset of symptoms and 3 years after surgery first advised. Carcinomatous ulcer, grade IV; lymph node metastases.

better, and the patient would have enjoyed the benefits of surgery that much sooner.

Figures 1 to 8, inclusive, illustrate some of the points brought out in the body of this paper and the legends speak for themselves.

DISCUSSION

It has always been true that any efforts to change old and established procedures handed down by our forefathers have met with resistance. This has been particularly true in

our profession, and rightfully so, because we are dealing with human life and certainly this demands a minimal of experimentation. Having lived through that period of renaissance in gastric surgery as related to the problems of the surgical management of duodenal ulcers, particularly the role of gastroenterostomy in their treatment, I can easily see why the present question of vagotomy is undergoing such bitter controversy. It is difficult to arrive at the truth of things, and only by prolonged application and observation can proper evaluation of any method be made.

As pointed out in the opening sentences of this article, with difficulty we keep abreast of the progress of surgery and the application of this progress to problems long considered to lie in the province of the internist. Certainly sufficient material has now been accumulated to prove beyond question of a shadow of a doubt that very few people survive for as long as 5 years, or even 3 years, who are operated upon when a preoperative clinical diagnosis of gastric cancer has been made. As Ochsner has said, the fact that only 10 per cent of all patients seen with gastric carcinoma are alive at the end of 5 years is indeed deplorable. It is even more deplorable in the experience of many other observers. The efforts that we have all made by total gastrectomy—including removal of the spleen, omentum, all available lymphatics, in the gastrohepatic mesentery and around the pancreas, not infrequently a part of the pancreas itself, the transverse colon, or portion of liver, and even a portion of the diaphragm—may be commendable in our present state of knowledge in our attempts to cope with this relentless marauder; but it leaves and will continue to leave a pitifully small percentage of people who survive in comfort long enough to be grateful to their surgeon for attempting such heroic measures in their behalf.

In our study of 140 consecutive gastric carcinomas (21) surviving gastric resection, 25 per cent were alive without evidence of recurrence at the end of 5 years, or longer. The important observation in this study, and the one most pertinent to this discussion, was that in none of these survivors was the pathologist able to demonstrate metastases to the regional lymph nodes or to other structures. If we are ever going to improve our statistics for surgery for gastric cancer in our present state of knowledge, it is going to be by operating on individuals in whom the diagnosis is made by the pathologist and his microscope, and not by the clinician by any methods of diagnosis at his disposal at the present time. Extending the radicalness of removal of the stomach is not the answer to this problem.

Statistics collected over long periods of time on an appreciable number of cases of small ulcerating lesions of the stomach to determine the ultimate outcome of conservative therapy have not been readily available. The results reported by the Mayo Clinic group and others should, it would seem, dampen the optimistic spirit of those who heretofore have been so enthusiastic about this method of approach to this problem. Fortunately for the patients who have come under our care we cannot, and will not in the future, I am sure, be able to assemble any large series of cases to throw further light on this important subject.

SUMMARY AND CONCLUSION

To briefly review the salient features of the data cited and which have the greatest practical application in the treatment of patients with ulcerating lesions of the stomach, the following points are worthy of emphasis.

1. One hundred per cent of gastric carcinomas prove fatal unless surgically removed.

2. No ulcer of the stomach, however innocuous it may appear to be by all methods of investigation now at our command, can be considered benign until proved so by microscopic study by a competent pathologist. Even study of serial sections may be necessary to rule out the possibility of malignancy.

3. From 10 to 20 per cent of all clinically benign ulcers ultimately prove to be malignant.

4. Results of attempts to cure or long alleviate the suffering of gastric cancer have in the majority of instances proved to be appallingly disappointing.

5. Improvement in these statistics will come about only when the diagnosis of cancer is made by the microscope and not preoperatively by the clinician.

6. The results of medical treatment of gastric ulcers have been disappointing and offer no assurance against the development of many serious complications.

7. Gastric resection for gastric ulcers is both a safe and satisfactory procedure.

8. An individual harboring a small gastric ulcerating lesion is 100 to 150 times more likely to have or ultimately to develop a gastric carcinoma than is the population as a whole.

And, finally, anyone cognizant of these facts must conclude that all ulcers of the stomach are a surgical problem from the moment such a diagnosis is made.

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THE REPLACEMENT OF SEGMENTS OF THE THORACIC ESOPHAGUS BY POLYTHENE TUBES

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THE excised esophagus can be successfully replaced by bowel, but there are times when it would be well to avoid such long and trying operations by the insertion of an inert tube between the esophageal ends, if it could be done with safety and without upset in swallowing.

The following facts suggested that such replacements might be successful, and the work to be described was done on rabbits to see if these ideas were correct. (1) It has been shown, when replacing sections of the thoracic aorta with polythene (6), that an adventitious capsule soon forms round the tube (within a few days). (2) The cervical esophagus can be replaced by an inert tube and will reconstitute an epithelial lining. It was hoped that the same thing would occur in the thorax. Temporary leaks with sinus formation do occur quite often in the neck which would be disastrous in the chest, however, it seemed possible that success might be achieved. (3) Food passes on when a segment of transverse colon is used to unite the stump of the stomach to the duodenum after partial gastrectomy, despite the fact that peristalsis in the colon is moving toward the stomach.

The experiments were begun in May, 1949, and the results are published now, although none were successful, in order to compare and contrast them with the excellent results obtained by Berman (1–5) in dogs and man, using identical methods.

PROCEDURE

Polythene tubing was used because it causes very little tissue reaction and, being nonwettable, food and fluids would be unlikely to stick to its inner surface.

The experiments were performed on rabbits as they are readily available and withstand intrathoracic procedures well. They were anesthetized with intravenous pentobarbitone (nembutal) using 50 to 65 milligrams per kilogram. The trachea was intubated blindly, and the animal maintained on artificial respiration with a small physiologic pump (6).

The chest was opened on the left side through the fifth, sixth, or seventh interspace, the ribs well separated, and the stroke volume of the pump adjusted so that the lungs just failed to collapse in expiration. The lung was then retracted, the esophagus exposed below the aortic arch, and the field packed off with swabs rung out in 1/1000 acriflavine. The esophagus was freed, a section excised, and the gap bridged with a piece of polythene tubing about 20 to 30 millimeters long and 8 millimeters in internal diameter.

No antibiotics were used in the majority of cases, for it was believed that a procedure was most dangerous if it depended upon them for success in animals. Antibiotics were used, however, in some cases, but without altering the final result.

The esophagus in the rabbit, below the aortic arch, has almost no mediastinal tissue around it, so that it was usually impossible to cover the tube with pleura or other supporting structures.

METHODS OF FIXING THE TUBE IN PLACE AND RESULTS (TABLE I)

1. The tube was inserted into the cut ends of the esophagus and kept in place with a simple ligature of linen thread. This procedure was carried out in 13 rabbits, in 11 with a straight tube and in 2 with the ends of the tube splayed to trumpet form.

In 5 rabbits no antibiotic was used; in 1 sulfanilamide was inserted locally; in 2 penicillin was used locally and parenterally; in 5 penicillin and streptomycin were used locally and parenterally.

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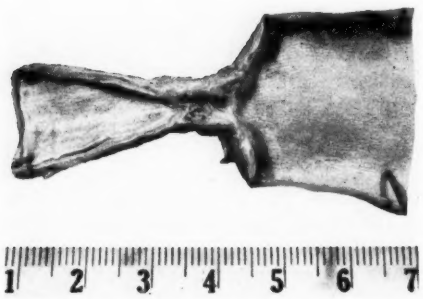


Fig. 1. Polythene replacement 27 days before. The tube had been passed. No leak had occurred but a stenosis developed with dilation and hypertrophy of the upper end of esophagus.

The longest survival period was 43 days; the shortest survival, 6 days; and the average survival, 18.4 days.

Twelve of the 13 rabbits were killed because of a local or general empyema which appeared only a few days before death, the rabbits being well until then.

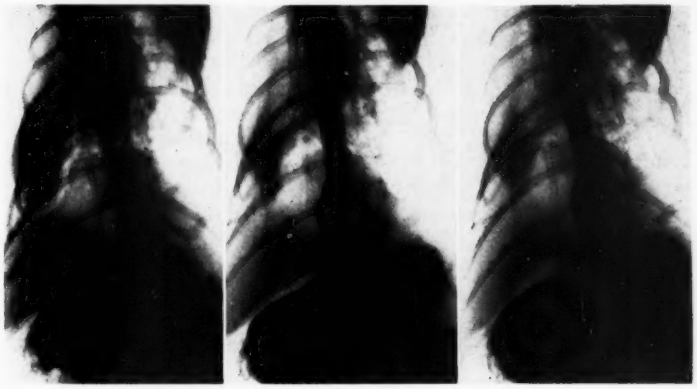
In 1 case (No. 8 killed at 27 days) the tube had been passed, the esophagus had united to the capsule, and no leak had occurred, but a stenosis developed (Fig. 1) and the animal had to be killed.

Local sulfanilamide or penicillin alone made no difference in survival, but penicillin and streptomycin locally and intramuscularly did

Fig. 2. Perforated polythene tube placed beside the esophagus and left for 42 days. Segment of esophagus excised and tied to a second tube (which has been removed) inside the first; this had been done 46 days before the rabbit was killed. Note the strong capsule growing round and through the perforations and the firm attachment of the esophageal ends to the new capsule. The upper end of the esophagus is dilated and hypertrophied. The inner tube was free and a leak had occurred.

TABLE I.—METHODS AND RESULTS

Rabbit No.	Procedure	Length of survival in days	Cause of death
1	Simple ligature to hold esophagus in place	42	Empyema
2		6	Empyema
3	Simple tie	9	Empyema
4		6	Empyema
5	Simple tie and sulfanilamide locally	9	Empyema
6	Simple tie and penicillin i.m.	15	Empyema
7		8	Empyema
8	Simple ligature to hold esophagus to tube and penicillin and streptomycin locally and parenterally	27	No leak; stricture; killed.
9		28	Empyema
10		28	Empyema
11		12	Empyema
12	As above and end of tube splayed out	6	Empyema
13		43	Empyema
14	Broad tape ties to hold esophagus ends	85	Empyema
15		10	Empyema
16		18	Empyema
17		4	Empyema
18	Tape sewed in position	3	Empyema
19	Polythene band or cover to hold esophagus upon tube	3	Empyema
20		8	Empyema
21		7	Empyema
22		7	
23	Fascial cover; esophagus ends tied to tube; fascia sewed to esophagus to cover tube and esophagus ends	2	Empyema
24		10	Empyema
25		6	Empyema
26		2	Empyema
27	Skin cover to tube	2	Empyema
28	Simple tie; penicillin and streptomycin and extraction of tube	Tube in 9 days; then removed; lived 1 day	
29		Tube in 7 days; then removed; lived 2 days	
30	2 stage with 15 days between	2	Empyema
31	2 stage with 17 days between	3	Empyema
32	2 stage with 28 days between	2	Empyema
33	2 stage with 7 days between	15	Empyema
34	2 stage with 42 days between	46	Empyema
35	2 stage with 28 days between	2	Empyema
36	2 stage with 28 days between	2	Empyema



a b c

Fig. 3. Barium swallow in a rabbit at 30 days after replacement. The exposures were at ½ second intervals. a, A bolus of barium approaching the tube, tube and lower esophagus empty, stomach contains barium. b, The tube, and the esophagus above and below the tube, filled with barium. c, Upper esophagus empty; tube and lower esophagus filled and barium entering stomach. This rabbit is the one whose esophagus is shown in Figure 4.

prolong life to an average of 27.6 days (as opposed to 12.6 days without), although the final result was the same.

Attempts were made to fix the ends of the esophagus with wide bands, the idea being that thus the ends of the esophagus would not be strangulated and would be held in place indefinitely. The methods used were: (a) broad ties of tape instead of linen thread; (b) broad bands of tape sewed in place instead of tied; (c) broad bands of polythene gently tied over the esophageal ends. (d) a complete outer cover of polythene.

No antibiotics were used.

In 4 cases in which tape ties were used the survival period was 85, 18, 10, and 4 days, respectively. In 1 case in which the tape was sewed in place the survival period was 3 days. In 4 cases in which polythene fixations were used the survival periods were 8, 7, 7, and 3 days.

The cause of death, in each case, was an infection in the chest.

The results seemed in no way to differ from the first method which is not surprising as it was impossible to hold the esophageal ends in place without strangulating them.

3. An autograft of fascia lata or skin was used to cover the tube and esophageal ends after the tube had been fixed in place with ligatures.

No antibiotics were used.

In 4 animals in which fascia lata was used the survival periods were 10, 16, 2, and 2 days. In 1 animal in which skin was used the survival period was 2 days.

The cause of death, as before, was empyema.

4. It seemed that the tube, acting as a foreign body, might be causing the leak, so an attempt was made to remove it before

Fig. 4. Thoracic esophagus. Polythene replacement 42 days before. The tube (which has been removed) had been inserted into the cut ends of the esophagus and fixed by a single ligature of silk. The esophageal ends are seen to be well attached to the new capsule which had formed round the tube. There is no gross dilation or hypertrophy of the upper esophagus. The tube itself was lying free inside the new capsule and a leak had occurred.

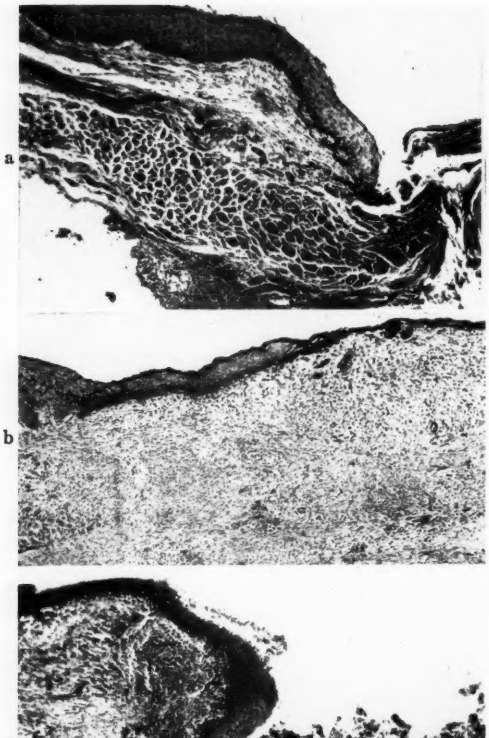


Fig. 5. Photomicrographs of sections taken longitudinally from upper esophagus across the new capsule to lower esophagus to show the growth of epithelium. a, Four days after implantation to show normal esophagus ending abruptly where the ligature had been placed. No epithelial growth as yet. ×60. b, Nine days after implantation. Note the epithelium growing vigorously from normal esophagus on the left across the capsule of granulation tissue. ×35. c, Forty-two days after implantation to show the termination of the epithelial growth—the upper and lower growth had not yet met (specimen shown in Fig. 1). ×35.

this occurred. The method was to put in a tube with simple ligatures and then remove it at about the time the ligatures could be expected to have cut through. The tube could be pulled out through the esophagus by using a child's bronchoscope as an esophagoscope.

This procedure was used in 2 cases. In one in which the tube was left in place 9 days and then extracted, the animal survived 24 hours. In the other in which the tube was left in place 7 days and then extracted, the animal survived 2 days.

It was found at necropsy that the extraction of the tube had torn the new capsule and a gross leak had occurred.

5. Although two stage procedures were opposed to the idea of the replacement, it was decided to try them and see the result. The method was to place a polythene tube, with multiple perforations in it, beside the esophagus and leave it until it was well encapsulated with tissue growing through the holes, and then to excise the esophageal segment as before and either suture the ends to the new covered tube or tie them to a second polythene tube inside the first (Fig. 2).

The period between the two stages varied from 1 to 6 weeks. No antibiotics were used.

The esophageal ends were sutured to a new tube in 4 rabbits, in which the survival periods after the second operation were 2, 2, 3, 2 days. The esophageal ends were tied to an inner tube in 3 rabbits, in which the survival periods after the second operation were 2, 15, 46 days.

The cause of death was the same, i.e. a local or general empyema.

PROGRESS FOLLOWING THE REPLACEMENT AND POSTMORTEM FINDINGS

Of the 36 rabbits, 13 developed a chest infection at once and died or were killed in 2 to 4 days, 13 lived from 6 to 12 days, and 10 lived from 15 to 85 days, with an average of 34.7 days. All but 1 dying or being killed because of an empyema.

The animals which survived the first few days swallowed well and maintained their weight until the chest infection occurred (Fig. 3), and, when killed, their stomachs were full of food.

It was found at necropsy that, in all the rabbits which lived more than a few days, a firm capsule had formed round the tube and esophageal ends (Fig. 4) and that the lung

was adherent to the site. Nevertheless, a leak had occurred with the production of a local or general empyema. The leak did not seem to be at the junction of esophagus and new capsule, but somewhere in the middle of the new capsule (Figs. 2 and 4). The tube itself was lying free inside the capsule, with fluid and food particles in and around it and, in one case, it was in an abscess cavity. The impression gained from these findings was that the tube was acting as an infected foreign body and perhaps causing the leak. The esophagus itself was normal below the stricture, but the upper end was usually slightly dilated (Fig. 4) and greatly dilated when a stricture formed. A stricture occurred, however, only when the tube ends and the junction of esophagus and new capsule coincided (Fig. 2) and in the case in which the tube had not been passed (Fig. 1). If the tube projected well into the esophagus, no stenosis developed (Fig. 4).

When the inside of the new capsule was examined, it was found to be smooth except where it communicated with the empyema. These specimens, taken from 4 to 85 days after implantation of the tube, were examined microscopically (Fig. 5), and it was found that the esophageal epithelium was growing from each end to line the new capsule, outside the polythene tube, in all but 1 at 4 days and 1 at 36. In no case had it completely bridged the gap. Berman (1) found that it took about 1 year in dogs to bridge a gap of 60 millimeters. The new epithelium varied from a thin layer to one which was irregular and hypertrophied.

DISCUSSION AND CONCLUSIONS

Segments of the thoracic esophagus in rabbits can be temporarily replaced by polythene tubing, and the best method seems to be simple ligatures to hold the esophageal ends upon the tube. Nevertheless a leak occurs sooner or later leading to an empyema. According to Berman, this does not occur in dogs or man and it is of interest to consider why our results should differ.

The method of fixing the tubes in place does not appreciably differ—Berman's method being essentially a simple ligature, with an added stitch, through two holes in a cuff on the tube, to stop retraction of the esophagus, and, in his latest method, a plastic cuff instead of a ligature to keep the esophagus in place.

The postmortem findings in the rabbits gave the impression that the tube itself, lying loose inside its new capsule, was acting as an infected foreign body, but Berman has had tubes in situ for months without trouble.

Berman (5) states in his description "...The mediastinal pleura, if it is not adherent, should be opened very carefully so that after implantation of the tube you will have a complete and solid closure of the mediastinum." This is impossible to do in rabbits, for the mediastinal tissue is practically nonexistent below the lung roots, so that there is not only no tissue to cover the tube on the side opened, but, often, an opening is made into the opposite pleural cavity as well. This, then, is perhaps the reason why the results differ so radically; but this explanation is not really satisfactory as the tube became walled off for long periods in several rabbits, but eventually an empyema developed.

It seems, therefore, that the different results must be attributed to the difference in resistance of the animals used—admittedly a poor explanation.

SUMMARY

Segments of the thoracic esophagus were replaced with polythene tubes in 36 rabbits.

The methods of fixing the cut ends of the esophagus to the tube are described.

A capsule forms round the tube and esophageal ends.

An epithelial lining grows from the cut ends of the esophagus to line the new capsule.

Despite the capsule and the epithelial lining, a leak with empyema formation occurred in all but 1 rabbit. The period of survival depended on the time of the leak—the longest being 85 days.

Swallowing was satisfactory although some dilatation and hypertrophy of the upper end of the esophagus occurred in those animals which survived long enough.

There was a strong tendency to stricture formation unless the tube crossed the junction of esophagus and capsule.

The differences between the results and those of Berman are considered, and an explanation of the differences attempted.

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PLACENTA PREVIA AND PREVIOUS LOWER SEGMENT CESAREAN SECTION

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DURING the course of an enquiry into the causes of bleeding in placenta previa based on all cases diagnosed at Mill Road Maternity Hospital, Liverpool (1), it was noted that several of the multiparas with placenta previa had had a previous lower segment cesarean section. In order to ascertain whether this was a chance finding or one of possible etiologic significance, all cases of placenta previa seen at all 5 hospital obstetric units in the city of Liverpool were reviewed. Subsequently through the good offices of Professor C. H. G. Macafee, access was obtained to the records of cases of placenta previa at the Royal Maternity Hospital, Belfast. Only those cases in which the placenta was felt or seen to involve the lower segment were included.

The periods covered, which were governed by the availability of records, were as follows:

Mill Road Maternity Hospital (M.R.M.H.) from October 1946 to December 1952
Liverpool Maternity Hospital (L.M.H.) from January 1947 to December 1952
Walton Hospital (W.H.), Broadgreen Hospital (B.H.), Sefton General Hospital (S.G.H.) } From January 1948 to December 1952
Royal Maternity Hospital, Belfast (R.M.H.) from January 1946 to December 1952

The incidence of placenta previa in Liverpool. There were 393 cases of placenta previa among the 66,427 deliveries in the 5 Liverpool hospitals during the time of review, an incidence of 0.6 per cent. These hospitals account for about 73 per cent of the total deliveries in the city of Liverpool each year. As practically all cases of placenta previa gravitate to a hospital, the incidence in the city, as opposed to in the hospitals, was in the region of 0.45 per cent. These figures relate to proved cases; but not all cases are proved, therefore, the true incidence of placenta previa must be some higher than these figures.

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Parity. Placenta previa occurs more often in multiparous women. Primigravidas comprised 41 per cent of the hospital deliveries in Liverpool, but only 16.5 per cent of cases of placenta previa, a figure comparable to the 18.8 per cent quoted by Macafee. The incidence for each parity has not been calculated, but the rates for the Liverpool hospital cases of placenta previa were 0.24 per cent in 27,235 primigravidas and 0.84 per cent in 39,192 multigravidas.

Age. Placenta previa occurs more often in older women; and the preponderance of multigravidas is almost certainly due to their greater average age, and not vice versa. For example, at M.R.M.H. women of 35 years of age or more accounted for 12 per cent of all deliveries but for 35 per cent of the cases of placenta previa. In primigravidas, too, placenta previa was more common in the older women. Of all the primigravidas delivered at M.R.M.H. only 2 per cent were 35 years of age or more, but of the primigravidas with placenta previa 23.5 per cent belonged to this older age group. These findings support the view of Penrose that increasing age is a significant factor in the incidence of placenta previa.

Previous obstetrical history. According to Greenhill, a disproportionately large number of women with placenta previa have previously had abortions and manual removal of the placenta. The latter point could not be investigated, but in this series 30 per cent of the multigravidas with placenta previa had previously had 1 or more miscarriages. This figure does not seem unduly high, for 26 per cent of all multigravidas delivered in the hospitals had such a history.

PREVIOUS CESAREAN SECTION

The total number of women with placenta previa is divided into 3 groups: 96 primigravidas, 19 multigravidas with abortions only, and 444 multiparas, a total of 559.

Considering the 444 multiparas only, it is noteworthy that 45 of them had had a previous cesarean section of the lower segment type. This proportion shows surprisingly little variation from hospital to hospital: at M.R.M.H. 7 lower segment sections in 89 multiparas with placenta previa; at L.M.H. 9 in 82; at W.H. 5 in 58; at B.H. 3 in 29; at S.G.H. 5 in 53; and at R.M.H. 16 in 133.

One of the patients at B.H. is of particular interest. In her case section for disproportion was performed in 1945. In 1946, before the period of this review, at repeat elective section a placenta previa was encountered. In 1949 a further elective repeat section was performed. At her fourth operation, also elective, in 1952, placenta previa was again found.

Indications. The indications for the original cesarean section varied widely: placenta previa in 16 cases; disproportion in 12, brow in 1, face in 1, large breech in 1 (15 cases), fetal distress in 4 cases, pre-eclampsia in 1, accidental hemorrhage in 1, hypertension in 1 (3 cases); postmaturity in 3 cases; inco-ordinate uterine action in 1; diabetes mellitus in 1; repeated stillbirths in 1; and unknown indication in 1 case.

As 16 of the 45 sections were performed for placenta previa it might be argued that these figures indicate that placenta previa recurs naturally rather than because of the presence of a scar in the lower segment. But, firstly, recurrent placenta previa is rare, or was so before the lower segment type of section was generally adopted; thus Dodd could find only 20 recorded cases in the literature. Secondly, only 1 of the 444 multiparas with placenta previa in this series had previously had a placenta previa and been delivered vaginally. Thirdly, there is the evidence of the placental site.

The placental site. When the placenta is situated in the upper segment of the uterus, it is equally likely to be implanted on the anterior as on the posterior wall as Reid indicated. But in placenta previa, the anterior wall of the lower segment is involved in only about 30 per cent of cases: of 393 Liverpool cases the placenta was situated anteriorly in 30 per cent, posteriorly in 50 per cent, centrally in 15 per cent, and laterally in 5 per cent; of 166 Belfast cases it was situated anteriorly in 27.5 per cent, posteriorly in 50 per cent, centrally in 15.5 per cent, and laterally in 7 per cent. Yet in 31 of the 45 cases of placenta previa following lower segment section (67 per cent), the anterior wall was involved, a significantly increased proportion. In 6 of these cases, the placenta was central but the anterior wall was involved to such a degree that the incision at repeat section cut into the placenta. The posterior wall was involved in 11 of the 45 cases and the lateral wall in 3.

Furthermore, taking the 16 cases of recurrent placenta previa, there is some shift in the location of the placenta previa in the recurrence after section: The placental site at original section was on the posterior wall in 6 instances, the central in 3, the anterior in 3, the lateral in none, and unknown in 4; at recurrence the site was on the posterior wall in 4 cases, the central in 4, the anterior in 7, lateral in 1.

Interval between previous section and the placenta previa. In 38 of the 45 cases, the section had terminated the pregnancy immediately preceding the placenta previa; in 3 cases 1 abortion intervened; in 2 cases 1 delivery, and in 2 cases 2 deliveries intervened. In 22 of the 45, the time interval between the section and the delivery of the pregnancy complicated by the placenta previa was not more than 2 years: 1 year in 4 cases; 2 years in 18; 3 years in 8; 4 years in 5; 5 years in 5; 6 years in 1; 7 years in 1; 8 years in 1; 9 years in 1; and 10 years in 1 case.

DISCUSSION

The incidence of previous lower segment section in 444 multiparas with placenta previa was 10 per cent. The control figure for Liverpool, that is the incidence of previous section in all multigravidas delivered in hospital during the same period, was 3.8 per cent, and some few of these sections may have been of the classical variety. Further, in 67 per cent of the 45 cases of placenta previa following section, the placenta involved the anterior surface of the lower segment, whereas in other cases of placenta previa the anterior wall was involved in only 30 per cent.

These facts and other figures given in the foregoing suggest that a lower segment section

scar may predispose to placenta previa occurring in a subsequent pregnancy, especially the one immediately following the section, and perhaps particularly if the time interval from delivery to delivery is 2 years or less.

No direct reference to the possible etiologic effect of previous lower segment section on subsequent placenta previa has been found, but there are a few reports which are indirectly related. Thus it is interesting to note that Hess, in a report of a case of placenta previa of a succenturiate lobe, asserts that "the frequent observation of low implantation of the placenta or frank placenta previa where deep lacerations of the cervix have been known to exist or extensive tracheloplasty has been done suggests the possibility that such trauma may predispose to subsequent placental attachment in that area." No supporting evidence is produced by Hess for this statement. All cases of deep cervical tears and cervicotomy at M.R.M.H. and L.M.H. in the period of 1946 to 1951 were followed, and in none of the 18 who became pregnant again was placenta previa observed. This is not surprising, for before the scar could affect subsequent placentation, the tear or incision would have to extend into the lower segment of the uterus causing an incomplete uterine rupture, a condition seen rarely and then often treated by hysterectomy.

There are several papers in the literature dealing with pregnancies subsequent to cesarean section, and recounting the proportion of these delivered by the vaginal route, but among these reports only that of Duckering details the indications for repeating the section. In 257 out of 445 cases (58 per cent) a repeat section was performed and in 7 of these the indication was placenta previa. Unfortunately the type of original section in these 7 cases is not given, but it can be calculated that the general incidence of placenta previa in her clinic was less than 0.8 per cent as against over 1.5 per cent in women who had had a previous section. In the Liverpool cases in this series the incidence of placenta previa in all deliveries was 0.60 per cent, in primigravidas 0.24 per cent, in all multigravidas 0.84 per cent, in multigravidas delivered in hospital the incidence was 0.79 per cent, but in multigravidas with a lower segment scar 2 per cent, a significant increase.

Further in comparing these figures, allowance must be made for the fact that all multigravidas with section scars are delivered in hospital but many normal multigravidas are delivered at home. Placenta previa, therefore, occurs about three times as often in multigravidas with a lower segment scar as in those without.

In view of these figures, it is tempting to speculate why a lower segment scar is likely to be covered by the placenta in a subsequent pregnancy. It is presumably possible that the vascularity of the region of the scar is so altered that if the site of a subsequent implantation is relatively low, the persistence of villi of the chorion leve in contact with the scar is encouraged, perhaps because of deeper penetration. In this context reference may be made to a paper by Kistner and associates reporting 9 cases of simultaneous placenta previa and placenta accreta. Seven of the 9 women were multiparas and 5 of these 7 had had one or more previous sections; the type of section is not specified in all cases but was lower segment in at least 2. The authors conjecture that "possibly the depth of trophoblastic extension was modified by the presence of a scar."

While on the one hand the placenta implanted on a section scar is thus thought to be more likely to be accreta, Wilson is intrigued by the possibility, first voiced more than 20 years ago, that "implantation over the scar area is more conducive to rupture, particularly of the classical scar"; and he therefore advises x-ray placentography whenever vaginal delivery is contemplated after previous section. It would seem good policy to perform such placentography in every pregnancy in a woman who has had previous section. None of the 45 cases of placenta previa following section in the present series was complicated by rupture of the uterus.

It is possible that subsequent low implantation of the placenta might be more likely if the incision in the uterus is not truly or completely in the lower segment. This in turn would be more likely to occur if the section were performed before the onset of labor, or

if the incision were vertical. A vertical incision was only exceptionally employed in Liverpool, but in at least 24 of the 45 cases in this series the section was performed before the onset of labor.

The significance of the relatively high incidence of a lower segment scar found in this series of multiparas with placenta previa could be assessed by similar figures being calculated for other large obstetric units. In particular a control figure could be obtained from hospitals where the classical type of section is still largely performed.

If the present figures are confirmed by others, several points of interest arise: Firstly, as the lower segment is increasingly the route of choice for section, the incidence of placenta previa may rise. Secondly, with an increasing proportion of cases of placenta previa being treated by lower segment section, the incidence of recurrent placenta previa may rise. Thirdly, a further reason becomes apparent why there should be no undue relaxation of the indications for cesarean section, an operation which always prejudices the woman's obstetric future. And fourthly, not only should every woman with a section scar always be delivered in hospital, but placentography is indicated in each pregnancy, especially in those instances in which vaginal delivery is contemplated.

SUMMARY

Of 444 multiparas with placenta previa, 45 had had a previous lower segment section. This proportion of 10 per cent seems unduly high.

Evidence is adduced suggesting that a lower segment section scar increases threefold the chance of placenta previa occurring in a subsequent pregnancy, especially the one immediately following the section and perhaps particularly if the time interval from delivery to delivery is 2 years or less.

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EDITORIALS

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MAY, 1954

DIAGNOSTIC LAPAROTOMY IN CHRONIC ABDOMINAL DISEASE

MODERN abdominal surgery is based upon principles which have evolved gradually over the last hundred years. Today, extensive ablations of viscera are undertaken in an attempt to eradicate advanced malignant disease or to relieve terminal suffering. Similarly, the serious and late complications of chronic inflammatory disease may create major technical difficulties that increase the hazards of abdominal operations. That these critical situations arise is partly due to the silent nature of certain disease processes and partly to our limitations in the interpretation of early signs and symptoms. Although the role of surgical exploration as a diagnostic procedure defies exact definition, nevertheless, certain broad principles and specific indications may be discussed.

With the advent of anesthesia and later of asepsis, surgeons of an earlier era were able to open the abdomen with increasing confidence that the patient would survive. As modern methods of investigation for abdominal disease were not available, exploratory laparotomy gradually became a recognized diagnostic procedure. In more recent years the increased accuracy in the detection of disease by x-ray examination and the developments of laboratory and endoscopic methods of investigation have provided the clinician with valuable diagnostic aids.

In the investigation of a patient, these ancillary services contribute materially in a positive or negative way to the diagnosis. In dealing with them, however, too much reliance should not be placed upon negative findings while early signs and symptoms which should arouse suspicion of hidden organic disease are overlooked. The tendency of patients to seek medical advice earlier in the course of illness when symptoms are vague and ill defined places a grave responsibility on the clinician. The differentiation between organic and functional disease is often extremely difficult at this stage of the patient's illness. Furthermore, there will always be a proportion of our patients with well established, chronic abdominal disease which defies recognition. Their complaints cannot be fitted into some classic grouping which, once recognized, establishes a diagnosis. History, physical examination, and routine laboratory studies may only suggest that the patient is ill with a condition primarily affecting the abdomen. In such cases, a diagnostic laparotomy may be necessary to determine the presence or absence of an organic lesion and to institute appropriate therapy. Biopsy, after direct visualization and palpation, is at times required to establish the final diagnosis of an intra-abdominal lesion.

Generally, the indications for surgical exploration are: unexplained abdominal pain, increasing debility, a mass in the abdomen, gastrointestinal bleeding, jaundice, ascites, chronic diarrhea, or unexplained fever associated with abdominal signs or symptoms.

Pain in the abdomen is a common complaint in the absence of organic disease. It may be functional in nature and associated with a depression or anxiety state. Yet it must be remembered that depression may follow pain and weakness. Root pain from arthritis or other organic lesions of the lower thoracic and lumbar spine and chronic myalgia of the anterior abdominal wall may confuse the clinical picture and contribute to errors in diagnosis. However, by applying a working knowledge of the pain patterns of disease, a correct diagnosis of the underlying condition may be achieved in a high proportion of cases. In the remainder, diagnostic difficulties persist in spite of a thorough investigation.

In cases of suspected biliary colic with *normal gallbladder visualization,* operation should be advised only after investigation has eliminated lesions in the right kidney, stomach, and duodenum with special emphasis on excluding posterior peptic ulceration. Surgery can, with advantage, be postponed until after the second attack when a reinvestigation should be undertaken. With the newer x-ray techniques, even a little gravel may be seen.

An exploratory laparotomy is often disappointing in a patient who complains of attacks of upper abdominal pain after cholecystectomy. This is particularly true when the history reports that a noncalculous gallbladder has previously been removed, when the attacks are not associated with jaundice, and when thorough investigation fails to provide an alternative diagnosis to common duct stone.

Persistent, deep boring epigastric pain associated with vague dyspepsia and weight loss in a patient over 55 years of age suggests carcinoma of the body of the pancreas. The diagnosis in these cases can be confirmed only by laparotomy or autopsy.

Painless jaundice calls for early exploratory laparotomy in cases in which the history and laboratory tests indicate the presence of an extrahepatic obstructive lesion.

The presence of persistent and *unexplained fever* associated with vague abdominal symptoms, anorexia, and debility may suggest intra-abdominal Hodgkin's disease, renal or hepatic cancer. Fever and wasting due to renal or gastrointestinal cancer, especially if there are metastases, may occur *without symptoms or demonstrable roentgenologic evidence suggesting disease in these organs.*

Every undiagnosed mass within the abdomen should be explored. A retroperitoneal tumor may be found which will respond to radiotherapy or a clinically inoperable cancer may, on closer examination, be resectable.

Exploratory laparotomy for recurrent or chronic gastrointestinal bleeding in the absence of a specific preoperative diagnosis is often disappointing. Yet despite the failure of history, clinical examination, endoscopy, and x-ray studies to reveal the nature or site of the lesion, the patient's condition may demand a laparotomy to complete the investigation.

Even with the newer techniques, 3 to 5 per cent of chronic penetrating peptic ulcers cannot be demonstrated by x-ray examination. This percentage increases sharply in flat, superficial ulcers, while recent acute erosions commonly go unrecognized. Unfortunately, the all too common label of a "functional gastrointestinal tract disorder" is placed on these patients because their pain pattern is atypical and variable and often associated with flatulence and constipation.

Granulomatous, neoplastic, and hemorrhagic lesions of the small bowel are notoriously diffi-

cult to diagnose in the early stages without exploratory laparotomy. Many cases of regional ileitis with chronic diarrhea are discovered only by laparotomy.

The word "abdomen" is derived from the Latin verb "abdere," to hide. It is true that many early serious and silent lesions are hidden within the abdominal cavity. With modern methods of investigation and expert consultation at his disposal, the abdominal surgeon should seldom have occasion to perform an exploratory operation. Yet, in selected cases, it may be the only method by which he may recognize or exclude serious organic disease. The decision to explore is influenced by a reasonable suspicion of cancer. If the possibility is strong, exploration should be proceeded with at once. In other cases, a period of observation is usually justified during which time a trial of medical management can be directed toward the control of symptoms. To avoid unnecessary exploratory operations and at the same time protect the patient from dangerous delay in cases of serious organic disease requires a close check on the clinical course of the patient's illness. In doubtful cases, a second history taken by another clinician may provide the clue to a correct diagnosis. Again, the radiologist is usually entitled to a "second look" before the surgeon proceeds with a laparotomy for purposes of diagnosis in suspected chronic abdominal disease.

P. H. T. THORLAKSON.

CAUSTIC BURNS OF THE ESOPHAGUS

IT IS difficult to recall any surgical lesion which produces more devastating results and at the same time is more easily avoided than caustic stricture of the esophagus. Except in cases of attempted suicide this condition is entirely preventable and only the smallest amount of common sense needs to be exercised to avoid its occurrence. To our knowledge there has never been an educational program to make individuals aware of this danger and the only legislation we can recall was to label containers properly. This latter is ignored not by the manufacturers but by the housekeepers who place the corrosive substances in receptacles which are familiar to the child, perhaps attractive, and often in very accessible places. These agents are commonly found on the floor in bathrooms and the precautions are lost on the child who is not able to read them. Lye is the most serious offender, also the commonest. It appears in various physical forms, solid, granular, or powder, all of which are caustic. The esophagus usually receives the brunt of the damage after ingestion. Strictly speaking, a child with a caustic burn of the esophagus is never normal again, regardless of the treatment. They might apparently lead a normal existence following treatment but the anatomic and physiologic relationships have been changed permanently.

There have been many articles in the literature on this subject, with several very comprehensive ones recently. Let us trace a case from ingestion to completion and try to organize our thoughts on the treatment of this condition. It will be found that there are great differences in opinion as to the management.

The emergency treatment, upon which there is agreement, consists of antidotes, treatment for shock if present, tracheotomy if there is edema of the larynx, and other such obvious procedures. The damage is usually done and the tissues destroyed irreparably at the time of the accident, just as in any other type of burn. The immediate problem is to maintain life and minimize the subsequent stricture formation. From this point there seem to be

two schools of thought. One is for early dilatation, which appears to be losing ground, and the other for delayed bouginage. The objections to each seem justified. The opponents of the immediate active treatment stress the danger of perforation and further trauma during the acute stage. Those opposed to the delayed treatment believe that valuable time is lost and that more scarring and constriction will result if active therapy is delayed. It is generally accepted that the treatment with antibiotics early is definitely indicated. Some advocate rest of the esophagus by performance of a gastrostomy for feeding which can also be used later for retrograde dilatation. Another group suggests an indwelling tube for 4 months. There can be no compromise with the conviction that these patients should be in the hands of a specialist from the beginning, one who is familiar with the treatment, and they should not be referred after long delay when firm stricture formation has developed. Following the acute phase it is generally agreed that dilatation should be performed at regular intervals. Various methods are used but this is more or less a technical point, up to the individual. All advise gentleness, of course.

The most recent contribution in the care of this condition is the introduction of cortisone, based on the knowledge that this drug has the tendency to inhibit fibroplasia. Much of this work has been done on an experimental basis and is promising from this standpoint. However, the chances of infection and perforation are more likely, hence it cannot be used without an added risk, and whether the beneficial results are sufficient to balance this danger remains to be seen. Scar tissue is a factor we never really have been able to control and it has been aptly said, "Once a stricture, always a stricture." There are certain to be strictures regardless of our efforts in many of these cases. Some of these strictures perhaps can be handled with dilatation and the child can eat normally but it is doomed to a lifetime of observation and potential obstruction.

It would appear that once a well developed stricture is present, the problem becomes surgical, which also raises the question as to the time and type of procedure that should be performed.

Gastrostomy as a final treatment is archaic and should be relegated to history except for purposes of emergency feedings or to establish a proper nutritional balance in preparation for a definitive procedure. The extremes in the time and type of treatment that we have encountered in the literature consist of 1 case which was resected 4 weeks after injury and another that was dilated for 60 years.

The methods for restoration of the continuity of the gastrointestinal tract consist of external esophagus with a skin or presternal intestinal tube, resection of the stricture with end-to-end anastomosis, by-passing or replacement of the esophagus with an intestinal tube, and resection of the strictured area with esophagogastrostomy. A prosthesis is not practical except as a palliative measure for a malignant lesion, and to our knowledge grafts have not been successfully utilized. Surgery in these cases is often difficult because the strictures are frequently high, multiple, or both, and there has been a rather severe degree of periesophagitis with firm and dense adhesions. Esophagogastrostomy removes the diseased tissue but replaces it with the hazard of esophageal ulceration which, if present, is in itself an extremely dangerous condition.

There is also some controversy as to the age when the stomach can be transferred into the thoracic cage without undue interference with nutrition and development. A recent report mentions a successful case without ill effects at the age of 17 months. The mortality rate of this operation is amazingly low and if the

disability following it, regardless of the age, is as minimal as those in the recently reported series, certainly it would appear that the therapy problem for this condition is answered. Resection, with anastomosis between the esophagus and stomach within the thorax which permits normal diet without untoward effects, is far preferable to restricted diet and repeated dilatations. It seems as if surgery is indicated as soon as a definite stricture of such a caliber as to interfere with swallowing is present.

In addition to the handicap and discomfort, the economic factor becomes almost prohibitive because of hospitalization costs when regular dilatations are performed. This is exclusive of any professional fees.

To those of us who have seen the ravages of esophageal burns, the thought cannot help but occur that something should be done from a publicity and educational standpoint to overcome this danger. The cliche, "An ounce of prevention is worth a pound of cure" was never more true. LEON J. LEAHY.

THE SURGEON AT WORK

A NEW INSTRUMENT TO FACILITATE TRANSDUODENAL SPHINCTEROTOMY

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THE sphincter of Oddi may be sectioned either endocholedochally by means of a special sphincterotome[1] or transduodenally. The latter procedure is mandatory if the common duct is too narrow for the insertion of the sphincterotome or when a probe cannot be passed easily into the duodenum. Although endocholedochal sphincterotomy is technically simple and rapid, it requires an intimate knowledge of the anatomy of the region, and gentle manipulation of the instrument. In addition, many surgeons prefer the transduodenal approach to avoid cutting the sphincter of Oddi "blindly," and also to be able to inspect the papilla for the possible presence of a neoplastic growth.

The main difficulty in the transduodenal approach, even after a catheter has been passed into the duodenum to locate the papilla is to bring the structure forward and expose it adequately for inspection and section. Traction sutures placed around the papilla tend to pull out, especially if only the mucosa had been caught by the suture, and the resultant bleeding obscures the field. Folds of mucosa, in the form of an overhanging cowl, make the accurate placement of the traction sutures difficult. Our technique up to the present has been to pass a curved probe down the common duct to the ampulla so as to elevate the papilla and push it through a small opening in the anterior duodenal wall. In order to overcome the trauma incident to the manipulation, rotation, and leverage of the metal probe a balloon catheter, which is the subject of this communication, was devised.

The catheter is 30 centimeters long and 3 millimeters in outside diameter. It can be made from a portion of a standard ureteral catheter or preferably of plastic material which can be boiled. A piece of fine steel tubing (part of a hypodermic needle), 1.5 centimeters long, is prepared by drilling a hole at its midpoint and closing one end. This steel tubing, just thin enough to fit into the lumen of the catheter, is pushed 15 centimeters down and fixed in position with a ligature tied around the catheter. The catheter is then pierced just over the hole in the steel tube. A piece of strong rubber tubing (red Dakin's tubing is adequate), 1.5 centimeters long, is positioned over the hole in the catheter and secured at each end by silk windings for a distance of 0.5 centimeter. This allows inflation of only 0.5 centimeter of the rubber tube. A stopcock is fastened at the distal end of the catheter. Slow injection of 1 cubic centimeter of saline with force will inflate the rubber so as to form a firm and turgid balloon (Fig. 1).

This balloon catheter can be passed down the cystic duct or through the common bile duct if the cystic duct is too narrow or has been removed at a previous operation. It passes into the duodenum readily. An incision 1.5 centimeters long is made in the anterior wall of the second portion of the duodenum and the end of the catheter is extracted with a tissue forceps. The little finger is then inserted into the duodenum along the catheter to the point at which it disappears through the papilla. The catheter is pulled down slowly until the uninflated balloon is felt passing through the papilla. This is pushed back just inside the papilla. At this point the balloon is inflated and is felt to distend the ampulla of Vater. Gentle traction on the catheter, while pushing the anterior duodenal wall backward, brings the papilla completely into view. The small opening in the duodenum is plugged by the protruding papilla preventing any spillage of duodenal contents.

When the papilla is thus exposed and under control, three traction sutures are placed, one inferiorly through the frenulum (plica longitudinalis) and one on each side of the ampulla. The

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[1] DOUBILET, H., and MULHOLLAND, J. The surgical treatment of recurrent acute pancreatitis by endocholedochal sphincterotomy. Surg. Gyn. Obst., 1948, 86: 295.

inferior suture must include the posterior duodenal wall since a mucosal suture will tear away and cause bleeding. Similarly, the sutures placed on each side of the ampulla must penetrate all three layers, passing through the duodenal mucosa, the sphincter muscle, and the ampullary mucosa, with the needle sliding along the inflated balloon but not into it.

The balloon is deflated and the catheter withdrawn, while the papilla is maintained in its position by the traction sutures. One jaw of an open straight mosquito clamp is then passed up the common duct for a distance of 1 centimeter. The clamp is then closed and tissues held in the jaws excised with a scalpel. The posterior wall of the ampulla is thus completely exposed, and if desired the opening of the pancreatic duct can then be located by watching for the flow of pancreatic juice, produced deliberately if necessary by the injection of secretin.

The cut edges of the common duct and duodenal mucosa must not be sutured since one of the stitches may occlude the pancreatic duct and produce acute pancreatitis postoperatively. The small incision in the duodenal wall is closed, the cystic duct is tied. No drainage is necessary. In the event that the common duct has been opened, a T tube with very short arms is sutured in place.

In the majority of cases of pancreatitis, the papilla is not involved in the fibrotic process which binds the duodenum to the diseased head of the pancreas and can be pulled anteriorly without difficulty. Occasionally, however, in advanced cases of chronic pancreatitis the enlarged head of the pancreas overhangs a retracted fixed papilla, rendering access to the region difficult. Under such conditions it is preferable to pass the sphincterotome from above and cut the sphincter under vision.

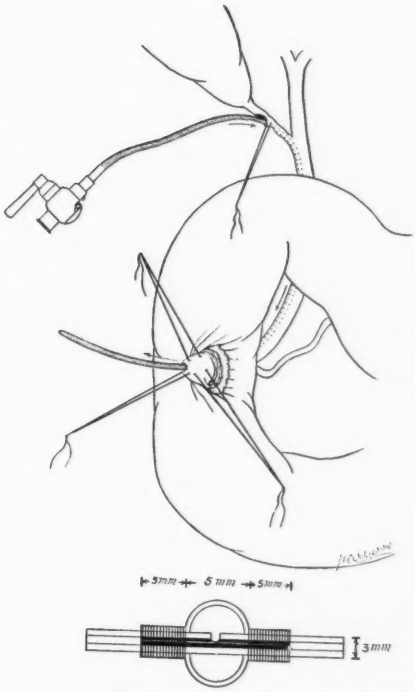

Fig. 1. The catheter is shown in situ with the balloon distending the ampulla. Traction on the catheter pulls the papilla through the small opening in the anterior duodenal wall. The 3 traction sutures have been inserted prior to deflation and removal of the tube. The detailed construction and dimensions of the balloon are shown in the insert.

THE SURGEON'S LIBRARY

REVIEWS OF NEW BOOKS

THE first edition of the book, *Human Embryology* in 1946, was justly acclaimed as a noteworthy contribution to the academic presentation of the morphologic aspects of development. It dealt wholly with human stages, no attempt being made to introduce material related to the comparative or experimental approach. This treatment found justification through not increasing further the size of a book already as large as a student text. A review of this edition of Bradley Patten's book may be found in this journal, volume 83, pages 678–679. To that evaluation little need be added with respect to the current edition,[1] for the reason that it is essentially a reprint of the original book. In Chapter 6 two new figures and an insert plate have been added; these are early embryos of the Hertig-Rock series. In the final chapter, 11 new and replacing figures are inserted dealing with the heart, aortic arch, and cardiac anomalies.

Except for the necessary comments related to the new illustrations, no changes in the text come to attention, and the pagination throughout remains, except for adjustments related to the new illustrations, as in the previous edition. The sizable bibliography has been augmented by a supplement, which contains entries covering the years 1945 to 1952.

This textbook still merits all the compliments it has received from this reviewer and others. It will continue as a standard source of information. Possibly the owner of a first edition may feel unable to justify its replacement, but all new purchasers will benefit to the extents already mentioned.

L. B. Arey.

EVERY reader who is interested in the origin and meaning of words will find both pleasure and helpful information in the stimulating and delightful *Source-Book of Medical Terms*[2] by Edmund C. Jaeger. Most medical men, and particularly those who were not exposed to Greek and Latin in college days, will agree with Dr. Irvine H. Page who says in his foreword, "I can only wish I had had this book in my youth to aid and guide me in unlocking the meaning and significance of the words which I have used so abundantly and, I fear, so carelessly."

This small volume (only 150 pages) is prefaced by a chapter entitled "How Words Are Formed," which includes a discussion of word stems both from Latin and Greek, and some simple rules concerning the forms and declensions of Latin nouns and adjectives to aid the student in using terms and phrases correctly, particularly as concerns number, gender, and case in compound names and phrases. The main portion of the volume is arranged alphabetically, and so well arranged that the student can quickly find the word stem, its source and meaning, with illustrative examples of its use. Prefixes and suffixes are included in the alphabetical arrangement and carefully defined.

A particularly interesting and delightful feature are the pen and ink sketches illustrating the origin of familiar terms, for example, the Latin *corax*, the raven, and *coracoid*, the beak like process of the scapula; the Greek *pellis*, bowl, and *pelvis* of the body and kidney.

We concur wholeheartedly with Dr. Page in "the hope that new students of medicine will start off in the proper use and appreciation of language" and the belief that "*A Source-Book of Medical Terms* will enliven and simplify the task" as well as the tasks of older students.

Sumner L. Koch.

THE fine handbook *The Fundamentals of Radiography*[3] is an excellent example of the contributions being made to medical personnel by industry. The text of this 100 page booklet is simple, brief, and adequate in providing a basic understanding of radiography to the student technician and resident radiologist. The illustrations are excellent and well chosen.

R. Burns Lewis.

FOR the general surgeon in the United States who can read German, *Allgemeine und spezielle chirurgische Operationslehre*[4], will be of value as an up to date summary of abdominal surgery in postwar Germany. The volume emphasizes briefly, but frequently, the contributions of various surgical authors with the dates. Thus, it is of considerable historic value.

[1] Human Embryology. By Bradley M. Patten. 2nd ed. 798 pages, 453 illustrations. $12.00. New York: The Blakiston Co., Inc., 1953.

[2] A Source-Book of Medical Terms. By Edmund C. Jaeger, D.Sc. Foreword by Irvine H. Page, M.D. 145 pages, illustrated. $5.50. Springfield, Ill.: Charles C Thomas, 1953.

[3] The Fundamentals of Radiography. Medical Division, Eastman Kodak Company. 8th ed. 100 pages, 45 illustrations. Rochester, New York: Eastman Kodak Co., 1953.

[4] Allgemeine und spezielle chirurgische Operationslehre. By Martin Kirschner. 2nd ed. Edited by N. Guleke and R. Zenker. Vol. VII, part 1—Die Eingriffe in der Bauchhoehle. New revision by Dr. Rudolf Zenker. Berlin: Springer-Verlag, 1951.

It is of interest to see what contributions have reached Germany from America and which authors are most quoted. A good example is the work of Allen Whipple on pancreatectomy. The use of drug therapy is stressed more than in most American texts. A special section gives careful consideration to antibiotics, their pharmacology and range of usefulness. The bibliography is placed in the back of the volume but is arranged by chapters.

As was the case with the old Kirschner, a special appeal to American readers lies in the illustrations. These are often semidiagrammatic but remarkably clear. They show a wide range of techniques and can be understood by those surgeons who do not read German easily.

The book stresses technique and states indications and contraindications, preoperative and postoperative care, and avoidance of complications. It, in general, does not tabulate results obtained nor is there as much evaluation of comparative methods as some readers might desire.

American surgeons will find it a useful addition to their libraries and for many it will signalize the re-establishment of German surgical literature.

JONATHAN E. RHOADS.

THE combined efforts of the members of the staff of the Pennsylvania Hospital are represented in *Clinical Obstetrics*[1]. Not only have members of the department of obstetrics and gynecology collaborated in the writing of this volume, but members of other departments have also contributed knowledge of their specialties pertaining to the obstetric patient. There is a discussion of current methods as practiced at the Pennsylvania Hospital, and equally vital, an analysis of new research in the field of obstetrics.

The material is well organized, with a division into nine sections. In the section on anatomy and physiology of reproduction, emphasis is definitely placed on the practical aspect of these basic sciences. Other sections deal with labor, abnormal labor, operative obstetrics, puerperal period, the newborn, and a final section treats with maternal and neonatal mortality, obstetric nursing practices, and legal aspects.

Robert Hingson has written the chapter on obstetric analgesia and anesthesia. Most of the study, as one might expect, deals with spinal and caudal anesthesia. Particularly helpful to the doctor practicing obstetrics is the listing of specific dosages of drugs used in analgesia and anesthesia.

Chapters on medical and surgical complications of the pregnant woman are treated briefly. Despite this brevity, many entities are mentioned and an outline of diagnosis and treatment set forth.

Compilation in one chapter of all laboratory data on the pregnant woman is a definite help to the practitioner and student alike. In no other place are these data for normal and abnormal problems so readily available.

The legal aspects of obstetric practice are treated in a pertinent chapter by Edward Hodge. Many phases of the problem are discussed in a brief, easily understood manner. The material presented should prove beneficial to all.

Paul H. Bishop has provided excellent detail in his chapter on obstetric roentgenology. He covers all aspects of the subject. The portion on soft tissue study is excellent.

This book is well written and very readable throughout. Excellent illustrations add much to the study of the text. The editor is to be congratulated on bringing the various topics together in a logical and practical manner. The work is one that will be of value to obstetrician, general practitioner, resident, and student and should win a prominent place on their bookshelves. WILLIAM R. ROACH.

THE handbook *Fundamentals of Clinical Cancer*[2] covers the treatment of neoplastic disease with particular emphasis given to radiotherapy. The author has produced a synopsis of malignant disease with special attention given to "those lesions which can be controlled." The entire presentation has suffered as a result of brevity. The introductory chapter on "General Considerations" establishes the fact that this book is planned to be very elementary. The remaining ten sections deal with the subject matter in accordance with the accepted anatomic divisions of systems. Each chapter has a very satisfactory bibliography to aid the more inquisitive reader. The photographs and diagrams are excellent.

The reader is impressed with the fact that both surgery and radiation are offered as alternative methods of therapy for many lesions and occasionally only the radiation aspect is developed. In a few instances radiotherapy is advocated where its use would be controversial, and at times both modalities of therapy are offered as satisfactory without sufficient clarification. For example, the section on breast tumors contains numerous indications for radiotherapy, either alone or in conjunction with some form of mastectomy. Among these are the size and number of palpable axillary nodes to be used in justifying preoperative irradiation. In discussing supplementary treatment of breast cancer the author states "Surgical castration is usually done for patients under 35 years while irradiation is done for those over 35." This arbitrary (and perhaps practical) attitude is also noted in the care of anal cancer, surgery being acceptable when the lesion is within the canal but roentgentherapy being suggested if it extended onto the perianal skin. Enthusiasm for both modalities was further demonstrated by the controversial

[1]CLINICAL OBSTETRICS. By Members of the Staff of the Pennsylvania Hospital. Edited by Clifford B. Lull, M.D., and Robert A. Kimbrough, M.D. Philadelphia, London, Montreal: J. B. Lippincott Co., 1953.

[2]FUNDAMENTALS OF CLINICAL CANCER; WITH EMPHASIS ON EARLY DIAGNOSIS AND TREATMENT. By Leonard B. Goldman, M.D. New York: Grune & Stratton, 1953.

statement that "liposarcoma may be treated by surgery or irradiation."

The section on the hypopharynx and the extrinsic larynx is very limited and characterized by the implication that a radiation cure rate of less than 15 per cent is the patient's only hope. The surgical developments pertaining to pharyngolaryngectomy with radical neck dissection are dismissed by the statement: "Surgery is seldom used because of the location."

The chapter on gynecologic tumors not only fails to outline symptomatology in a definitive manner but the treatment suggested is not always in accord with commonly accepted gynecologic concepts. For example, carcinoma of the vulva is almost universally thought to be best treated by excision and yet roentgentherapy for vestibular mucosal lesions is offered. While the treatment of cervical lesions is satisfactory the use of radium in carcinoma of the endometrium is poorly defined. The section on ovarian tumors leaves much to be desired.

While this text could be used as an introductory volume for the student, and some sections provide adequate guidance for the busy practitioner, in general the presentation is incomplete and lacks balance. WALTER W. CARROLL.

BY partial gastrectomy, the author[1] refers to the surgical removal of ⅔ or ¾ of the stomach and part of the duodenum. Because of this extensive surgery it is believed that "partial gastroduodenostomy" is the more appropriate term, and should supplant "partial gastrectomy."

Gastrectomia parcial; resultados na úlcera gástrica e duodenal reviews from a critical, analytic viewpoint the various methods of routine diagnosis, the indications and technique of partial gastrectomy as presently employed, and the aftermath of a disturbed physiologic process. The complicating sequelae are enumerated, as well as the safeguards against them.

A complete chapter is devoted to the comparative study of gastrectomy with and without vagotomy.

The book is divided into three parts and is based upon 100 cases, 20 of which are gastric ulcer patients. The remaining 80 cases are catalogued as duodenal ulcer patients. In the latter when there is a high hydrochloride gastric content, removal of ¾ to ⅞ of the stomach is recommended. When lesions are on the lesser curvature ⅔ of the stomach may be removed with confidence as to the outcome.

Eighty per cent of the patients had the Reichel-Polya type of anastomosis supplemented with a gastrojejunostomy, whereas the remaining 20 per cent had the Hofmeister-Finsterer procedure.

The results indicated that 78 per cent of the patients had satisfactory symptom relief, 20 per cent were improved, and 2 per cent were classified as not improved, or another ulcer followed the surgical procedure.

The mortality rate was only 1 per cent.

Because of the numerous charts and the complete documentation, the book is well received and easily read. A summary at the end of each chapter is most helpful. The author presents his thesis clearly and with candor, for which reason the book is highly acceptable. STEPHEN A. ZIEMAN.

READING *The Physical Examination of the Surgical Patient*[2] is a refreshing and stimulating experience, one well worth the modest expenditure of time and effort to any physician in active practice. The purpose of the book is to present in concise and systematic form the physical manifestations of surgical disease and the simple techniques of eliciting pertinent findings. The book is logically divided into the elective examination and the emergency examination. Under these two broad headings the authors present their material in separate chapters for each region of the body. The largest single chapter, that on examination of the abdomen, consists of five sections devoted to the elective examination, the appraisal of abnormal findings, the acute abdomen, differential signs in the acute abdomen, and the postoperative abdomen. The subsequent chapter deals with the examination of the abdomen of infants and children.

The authors have studied a great deal of material, culled from it the best and most significant information, and presented it in excellent sequence. No one field of diagnosis receives more than its fair share of space. The style of writing is simple, smooth flowing, and easy; it reflects complete familiarity with the subject. The authors' philosophy of the proper conduct of physical examinations and of the physician's relationship to the patient is well stated at the beginning of the book and is subtly evident throughout the volume.

The book contains a generous number of good line drawings, an appended check list for the physical examination, and a bibliography covering some of the finest articles written on the examination of surgical patients. The index is comprehensive—an invaluable feature in a book which is certain to be widely used as a reference work.

BENJAMIN F. LOUNSBURY.

THERE is no more difficult task than writing a small, concise treatise about a big subject. When Colby's original volume, *Essential Urology*,[3] appeared in 1950, it was immediately obvious that he had accomplished the difficult task admirably. The book is designed especially for the student, to give

[1] GASTRECTOMIA PARCIAL; RESULTADOS NA ÚLCERA GÁSTRICA E DUODENAL. By Lúcio Galvão. 163 pages, with 34 illustrations. Rio de Janeiro, 1952.

[2] PHYSICAL EXAMINATION OF THE SURGICAL PATIENT. By J. Englebert Dunphy, M.D., F.A.C.S., and Thomas W. Botsford, M.D., F.A.C.S. 326 pages, 188 illustrations. $7.50. Philadelphia, London: W. B. Saunders Co., 1953.

[3] ESSENTIAL UROLOGY. By Fletcher H. Colby, M.D. 2nd ed. 650 pages, with 352 illustrations. $8.00. Baltimore: The Williams & Wilkins Co., 1953.

him a clear view of the field of urology, undistorted by a mass of detail and controversial material.

The book is more than an outline. It presents the subject of urology in a condensed, crisp, yet surprisingly inclusive manner. A carefully selected list of key references accompanies each chapter, so that the student desiring more extensive information may quickly refer to the best articles that have been written on any particular subject. Emphasis has been placed on basic aspects, such as embryology, anatomy, physiology, and pathology.

Part 1 includes embryology, anatomy, and physiology of the genitourinary organs. Part 2 consists of a discussion of the examination of the urologic patient, with an excellent summary of pertinent laboratory procedures. Part 3 gives a description of the diseases of the genitourinary organs, the subject matter being classified on the basis of organs of the genitourinary tract, rather than diseases. Emphasis is placed on pathology, abnormal physiology, and diagnosis. Treatment is discussed only briefly because (being so often surgical) it is a subject for the more advanced or postgraduate student. However, an honest evaluation of various available methods of treatment is briefly outlined for the student.

The changes made in the second edition are not great. However, new material and new illustrations have been added where necessary to bring the subject up to date. Deserving of special mention in this regard is the section on tuberculosis of the genitourinary tract, which has been completely rewritten in the light of the great changes which have occurred as the result of modern antimicrobial therapy. Of importance also is the fact that references have been added to keep the student abreast of the current literature. This is one of the most important functions of this book.

Essential Urology has filled a long-felt need in urology. It is gratifying to see that the author is keeping the book alive and up to date. It is a "must" in reading for every student beginning the study of urology.

JOHN L. EMMETT.

IN Levitt's *Handbook of Radiotherapy*[1] he has lived up to the opening sentence in the preface and written an outline of radiotherapy addressed to the senior and postgraduate medical student. His simple nontechnical language can be understood by all. The definition and explanations of various types of radiant energy are simple and easily understood. The action of radiant energy on cells and types of disease is outlined according to the present conception. In the chapter on radiation sickness it seems that he is almost explaining it to the patient, thus giving a very clear picture of the problems.

The various techniques of applying radiation are discussed, and the accepted uses of radioactive isotopes are given.

The outline of the disease of the various parts of the body in order gives one a clear picture as to how each may be treated by radiation, surgery, or combinations of these.

The author definitely points out in many places contraindications to treatment and complications that develop. On the whole there is an enormous amount of information in this handbook presented in a very useful form.

F. H. SQUIRE.

IN a clear and concise manner *Inhalation Therapy and Resuscitation*[2], with frequent quotations from authoritative sources, presents the modern trends in inhalation therapy and resuscitative measures. The table of contents is an excellent skeletal outline amplified by a well organized bibliography. It defines, revises, and clarifies the terms pertinent to the changing concepts of disturbed physiology as related to respiration and oxygen want.

The first part of the book is concerned with the history, terminology, physiology, pathology, symptomatology, and indications for oxygen therapy and resuscitation. Particularly noteworthy is the brief, direct discussion of the physiology of respiration with a reclassification of hypoxia into seven groups on the basis of the etiology. The second part is devoted to methods of treatment and resuscitation. The chapter on "Methods" discusses the gas supply, fire hazards, and all types of apparatus. All methods of resuscitation are described in detail. Comments on the general care of the patient needing resuscitative measures are poignantly presented. The logical drawing together of the facts and methods of this book fills a need for physicians in any field of medicine.

LUCILLE WATT.

THE two volume edition on *Operative Surgery*[3] by Horseley and Bigger has been most interesting to the reviewer because he possesses a copy of the one volume second edition published in 1924. This second edition has been the most practical and useful textbook in my library. In the one volume book by J. Shelton Horseley, Sr., it was stated in the preface that every operation described was one that the author had done or, in unusual situations, it was an operation that appeared to him to be the one best suited for the disease. This statement offered confidence to the reader. The same general pattern has been followed in the sixth edition by the surgeons who have made the contributions on their particular subjects. In some general statements in the first chapter of this book, Horseley states that if we could get away from blindly following what someone says

[1] A HANDBOOK OF RADIOTHERAPY. By Walter M. Levitt, M.D., F.R.C.P.(Lond.), F.F.R., D.M.R.E.(Camb.). 232 pages, with 53 illustrations. $6.50. New York: Paul B. Hoeber, Inc., Medical Book Dept. of Harper & Bros., 1953.

[2] INHALATION THERAPY AND RESUSCITATION. PUBLICATION NO. 156, AMERICAN LECTURE SERIES. A MONOGRAPH IN THE BANNERSTONE DIVISION OF AMERICAN LECTURES IN ANESTHESIA. By Meyer Saklad, M.D. Edited by John Adriani, M.D. 343 pages, 110 illustrations. $7.50. Springfield, Ill. Charles C Thomas, 1953.

[3] OPERATIVE SURGERY. By Guy W. Horseley, B.S., M.D., F.A.C.S., and Isaac A. Bigger, M.D., F.A.C.S. Vols. I and II. 6th ed. 1,579 pages, with 1,274 illustrations. $30.00. St. Louis: The C. V. Mosby Co., 1953.

and do things because of reasons that have sound biologic foundations, we should undoubtedly do work more satisfactory to our patients and to ourselves. This is fundamental and in this day of many books, many periodicals, and many abstracts on surgery, the surgeon can forget to think and be too easily led into useless operations and complicated techniques.

On surgical drainage, there is an excellent discussion for the student, and a fine review for the practicing surgeon. The remarks on sutures and instruments are fundamental and there are good illustrations. It is profitable to read the chapter on malignant tumors because it is a good fundamental discussion of cancer. The pages on anesthesia emphasize the use of demerol as a preoperative medication because it is not only a sedative but has some atropine-like action and mimics papaverine in relaxing smooth muscle. Also there is emphasis on the value of ether and other inhalation anesthetics in cases of bronchial asthma not fully appreciated by many surgeons. A great number of pages are devoted to the various phases of plastic surgery and can be profitably read. There is an excellent discussion on the old methods and medicaments used in infections which still hold in this day of antibiotics and chemotherapy. Some chapters in the book could use a few more illustrations and other chapters are particularly well illustrated. Statements are direct, simple, and easily understood, and only occasionally is detail lacking in both words and illustrations. There is a good discussion on thoracic surgery and some phases are very well illustrated. The subject of esophageal diverticulum is particularly well presented and this holds true with reference to the entire discussion concerning the esophagus. The authors should be commended for their excellent discussion of surgery of the mammary gland and for the emphasis on advocating a separate higher incision in the management of sliding inguinal hernia. There is an impressive description of abdominal incisions but the authors fail to recommend delayed closure following wound evisceration or dehiscence.

Diseases of the gastrointestinal tract are very well handled although there would not be complete agreement on the use of sutures as described for ileostomy. The subject of proctology is well handled. One finds the chapter on the pancreas and spleen interesting, practical, and well illustrated. A number of chapters deal with bone and joint surgery and the comments made should be helpful to the general surgeon. Likewise the urological tract is discussed in a manner practical for the general surgeon and should prove interesting and valuable to the urologist. A number of chapters are devoted to the subject of gynecology. Some of these are excellent. More than a few surgeons would disagree with the statement that the intra-abdominal operation is no longer used as part of the treatment of prolapse of the uterus except by a few operators. The technique for vaginal hysterectomy is well illustrated but its value is probably emphasized too much. Simple lesions of the cervix are well discussed. There is a particularly good discussion of endometriosis. The subject of neurologic surgery is well covered. Although the general surgeon has gradually become more reluctant to undertake the management of neurologic conditions, the fundamentals and basic information are there for the general surgeon who must care for these cases.

These two volumes are easy reading, practical, have a wealth of information useful for the general surgeon, and many chapters would be of value to the specialist in the field. The student, the younger surgeon, and the experienced surgeon would profit by having them in his library. R. RUSSELL BEST.

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

ACTA CHIRURGICA SCANDINAVICA. Supplementum 182. The Effect of Cortisone on the Formation of Tendon Adhesions and on Tendon Healing; an Experimental Investigation in the Rabbit. By Nils Carstam. 111 pages, 23 illustrations. Stockholm: Acta chirurgica scandinavica, 1953.

EXPERIMENTAL SURGERY; INCLUDING SURGICAL PHYSIOLOGY. By J. Markowitz, M.B.E., M.B.(Tor.), Ph.D., M.S. in Exp. Surg.(Minn.). 3rd ed. 851 pages, 554 illustrations. $10.00. Baltimore: The Williams & Wilkins Co., 1954.

THE THYROID; A PHYSIOLOGICAL, PATHOLOGICAL, CLINICAL AND SURGICAL STUDY. By T. Levitt, M.A., F.R.C.S.(Eng.), F.R.C.S.(Ed.), F.R.C.S.I. 606 pages, 502 illustrations. $20.00. Baltimore: The Williams & Wilkins Co.; Edinburgh and London: E. & S. Livingstone, Ltd., 1954.

ULCERATIVE COLITIS; AND ITS SURGICAL TREATMENT. By Bryan N. Brooke, M.Chir., F.R.C.S. 147 pages, 89 illustrations. Baltimore: The Williams & Wilkins Co.; Edinburgh and London: E. & S. Livingstone, Ltd., 1954.

DIE OBJEKTIVE STEREOSKOPIE AN ROENTGENBILDERN; EINE DIAGNOSTISCHE METHODE. By Prof. Dr. A. Hasselwander. 187 pages, 125 illustrations. DM 27. Stuttgart: Georg Thieme Verlag, 1954.

GYNAECOLOGICAL AND OBSTETRICAL ANATOMY AND FUNCTIONAL HISTOLOGY. By C. F. V. Smout, M.D., M.R.C.S., and F. Jacoby, M.D., Ph.D. 3rd ed. 336 pages, 185 illustrations. $7.00. Baltimore: The Williams & Wilkins Co., 1954.

APPLIED CYTOLOGY. By G. R. Osborn, M.B., B.S.(Melbourne). 168 pages, 131 illustrations. 35s. net. London: Butterworth & Co., Ltd., 1953.

CARCINOMA OF THE COLON. By Leland S. McKittrick, B.S., M.D., F.A.C.S., and Frank C. Wheelock, Jr., A.B., M.D., F.A.C.S. 94 pages, 12 illustrations. $3.25. Springfield, Ill.: Charles C Thomas, 1954.

DIE ZENTRALNERVOESEN WIRKUNGEN VON HEILMITTELM. By E. Rothlin. 39 pages, 7 illustrations. DM 2.40($0.60). Stuttgart: Georg Thieme Verlag, 1954.

SURGICAL INFECTIONS; PROPHYLAXIS—TREATMENT—ANTIBIOTIC THERAPY. By Edwin J. Pulaski, M.D., D.M.Sc.(Surgery). 332 pages, 10 illustrations. $7.75. Springfield, Ill.: Charles C Thomas, 1954.